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APPLICATION NUMBER: 60/489,659

FILING DATE: July 23, 2003

RELATED PCT APPLICATION NUMBER: PCT/US03/34655

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV 329 308 388 US

21909 U.S. PTO
60/489659

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<input type="checkbox"/> Additional inventors are being named on the _____ Separately numbered sheets attached hereto			
TITLE OF THE INVENTION (500 characters max)			
SYNTHETIC PROCESS FOR TRANS-AMINOCYCLOHEXYL ETHER COMPOUNDS			
Direct all correspondence to: CORRESPONDENCE ADDRESS			
<input checked="" type="checkbox"/> Customer Number		 * 2 0 8 7 2 *	
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City		State	Zip
Country		Telephone	Fax
ENCLOSED APPLICATION PARTS (check all that apply)			
<input checked="" type="checkbox"/> Specification Number of Pages		28	<input type="checkbox"/> CD(s), Number
<input checked="" type="checkbox"/> Drawing(s) Number of Sheets		42	<input type="checkbox"/> Other:
<input checked="" type="checkbox"/> Application Data Sheet. See 37 CFR 1.76 - 2 pgs			
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT			
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27.		FILING FEE AMOUNT (\$)	
<input type="checkbox"/> A check or money order is enclosed to cover the filing fees		160.00	
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.			
<input checked="" type="checkbox"/> No		<input type="checkbox"/> Yes, the name of the U.S. Government agency and the Government contract number are:	

Respectfully submitted,

SIGNATURE

Michael R Ward

Date July 23, 2003

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REGISTRATION NO.
(if appropriate)

38,651

TELEPHONE

415/268-6237

Docket Number:

554793000200

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

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Dated: 7/23/2003 Signature:

(Lilla Olsen)

SF-1539612

EV329308388US

Application Data Sheet**Attorney Docket: 554793000200****Inventor Information**

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sf-1539631

Initial: July 23, 2003

Application Information

Title Line One:	SYNTHETIC PROCESS FOR
Title Line Two:	TRANS-AMINOCYCLOHEXYL
Title Line Three:	ETHER COMPOUNDS
Total Drawing Sheets:	42
Formal Drawings?:	Yes
Application Type:	Provisional
Docket Number:	554793000200

Representative Information

Representative Customer Number:	20872
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Continuity Information	N/A
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This application is a:
> Application One:
Filing Date:

which is a:
>>Application Two:
Filing Date:

which is a:
>>>Application Three:
Filing Date:

Prior Foreign Applications	N/A
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Foreign Application One:
Filing Date:
Country:
Priority Claimed:

SYNTHETIC PROCESS FOR TRANS-AMINOCYCLOHEXYL ETHER COMPOUNDS

FIELD OF THE INVENTION

The present invention is generally directed toward a process for the preparation of stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexyl ether compounds and a process for the preparation of stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexyl ether compounds as well as various intermediates and substrates involved. The compounds are useful for treating medical conditions, including, for example, cardiac arrhythmia, such as atrial arrhythmia and ventricular arrhythmia.

BRIEF DESCRIPTION OF THE DRAWINGS

Scheme 1 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexyl ether compound of formula (9).

Scheme 2 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (18).

Scheme 3 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (18).

Scheme 4 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (18).

Scheme 5 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexyl ether compound of formula (9).

Scheme 6 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (18).

Scheme 7 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (18).

Scheme 8 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (18).

Scheme 9 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexyl ether compound of formula (9).

Scheme 10 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexyl ether compound of formula (9).

Scheme 11 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (18).

Scheme 12 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (18).

Scheme 13 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexyl ether compound of formula (9).

Scheme 14 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexylether compound of formula (18).

Scheme 15 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (7).

Scheme 16 illustrates general a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (7).

Scheme 17 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (16).

Scheme 18 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (16).

Scheme 19 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (16).

Scheme 20 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (4) and a stereoisomerically substantially pure compound of formula (5).

Scheme 21 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (11) and a stereoisomerically substantially pure compound of formula (12).

Scheme 22 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (10) and a stereoisomerically substantially pure compound of formula (13).

Scheme 23 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (11) and a stereoisomerically substantially pure compound of formula (10).

Scheme 24 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexyl ether compound of formula (20).

Scheme 25 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (22).

Scheme 26 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (22).

Scheme 27 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (22).

Scheme 28 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexyl ether compound of formula (20).

Scheme 29 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (22).

Scheme 30 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (22).

Scheme 31 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (22).

Scheme 32 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexyl ether compound of formula (20).

Scheme 33 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexyl ether compound of formula (20).

Scheme 34 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (22).

Scheme 35 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (22).

Scheme 36 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexyl ether compound of formula (20).

Scheme 37 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexylether compound of formula (22).

Scheme 38 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (19).

Scheme 39 illustrates a general reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (19).

Scheme 40 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (21).

Scheme 41 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (21).

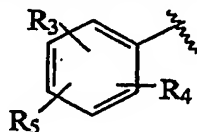
Scheme 42 illustrates a reaction scheme that may be used as a process for preparing a stereoisomerically substantially pure compound of formula (21).

DESCRIPTION OF THE INVENTION

The present invention is generally directed toward a process for the preparation of stereoisomerically substantially pure trans-(1*R*,2*R*)-aminocyclohexyl ether compounds and a process for the preparation of stereoisomerically substantially pure trans-(1*S*,2*S*)-aminocyclohexyl ether compounds as well as various intermediates and substrates involved. The final products are useful for treating medical conditions, for example, cardiac arrhythmias, including atrial arrhythmia and ventricular arrhythmia, as disclosed in PCT CA99/00280, incorporated herein by reference in its entirety. The intermediate compositions and may also be used to produce the final medically useful compound or other intermediates thereof.

Definitions and Conventions

In the formulae depicted herein, a bond to a substituent and/or a bond that links a molecular fragment to the remainder of a compound may be shown as intersecting one or more bonds in a ring structure. This indicates that the bond may be attached to any one of the atoms that constitutes the ring structure, so long as a hydrogen atom could otherwise be present at that atom. Where no particular substituent(s) is identified for a particular position in a structure, then hydrogen(s) is present at that position. For example, compounds of the invention containing the following group:



are intended to encompass groups wherein any ring atom that could otherwise be substituted with hydrogen, may instead be substituted with either R₃, R₄ or R₅, with the proviso that at least two of the positions are not substituted with any of R₃, R₄ and R₅. Ring atoms that are not substituted with any of R₃, R₄ or R₅ are substituted with hydrogen. In those instances where the invention specifies that a non-aromatic ring is substituted with more than one R group, and those R groups are shown connected to the non-aromatic ring with bonds that bisect ring bonds, then the R groups may be present at different atoms of the ring, or on the same atom of the ring, so long as that atom could otherwise be substituted with a hydrogen atom.

When the invention specifies the location of an asymmetric divalent radical, then that divalent radical may be positioned in any possible manner that provides a stable chemical structure.

The compounds of the present invention contain at least two asymmetric carbon atoms and thus can exist as enantiomers and diastereomers. Unless otherwise noted, the phrase "stereoisomerically substantially pure" generally refers to those asymmetric carbon atoms that are described or illustrated in the structural formulae for that compound.

The phrase "independently at each occurrence" is intended to mean (i) when any variable occurs more than one time in a compound of the invention, the definition of that variable at each occurrence is independent of its definition at every other occurrence; and (ii) the identity of any one of two different variables (e.g., R_1 within the set R_1 and R_2) is selected without regard of the identity of the other member of the set. However, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

In accordance with the present invention and as used herein, the following terms have meanings as generally understood to those of skill in the art, or are defined to have following meanings:

"Acid addition salts" refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid and the like.

"Acyl" refers to branched or unbranched hydrocarbon fragments terminated by a carbonyl $-(C=O)-$ group containing the specified number of carbon atoms. Examples include acetyl (Ac) $[CH_3C(=O)-]$, a C_2 acyl and propionyl $[CH_3CH_2C(=O)-]$, a C_3 acyl.

"Alkanoyloxy" refers to an ester substituent wherein the non-carbonyl oxygen is the point of attachment to the molecule. Examples include propanoyloxy $[(CH_3CH_2C(=O)-O)-]$, a C_3 alkanoyloxy and ethanoyloxy $[CH_3C(=O)-O-]$, a C_2 alkanoyloxy.

"Alkoxy" refers to an O-atom substituted by an alkyl group, for example, methoxy $[-OCH_3]$, a C_1 alkoxy.

"Alkoxyalkyl" refers to a alkylene group substituted with an alkoxy group. For example, methoxyethyl $[CH_3OCH_2CH_2-]$ and ethoxymethyl $[CH_3CH_2OCH_2-]$ are both C_3 alkoxyalkyl groups.

"Alkoxy carbonyl" refers to an ester substituent wherein the carbonyl carbon is the point of attachment to the molecule. Examples include ethoxycarbonyl [$\text{CH}_3\text{CH}_2\text{OC}(=\text{O})-$, a C_3 alkoxy carbonyl] and methoxycarbonyl [$\text{CH}_3\text{OC}(=\text{O})-$, a C_2 alkoxy carbonyl].

"Alkyl" refers to a branched or unbranched hydrocarbon fragment containing the specified number of carbon atoms and having one point of attachment. Examples include *n*-propyl (a C_3 alkyl), *iso*-propyl (also a C_3 alkyl), and *t*-butyl (a C_4 alkyl). Methyl is represented by the symbol Me or CH_3 .

"Alkylene" refers to a divalent radical which is a branched or unbranched hydrocarbon fragment containing the specified number of carbon atoms, and having two points of attachment. An example is propylene [$-\text{CH}_2\text{CH}_2\text{CH}_2-$, a C_3 alkylene].

"Alkylcarboxy" refers to a branched or unbranched hydrocarbon fragment terminated by a carboxylic acid group [$-\text{COOH}$]. Examples include carboxymethyl [$\text{HOOC}-\text{CH}_2-$, a C_2 alkylcarboxy] and carboxyethyl [$\text{HOOC}-\text{CH}_2\text{CH}_2-$, a C_3 alkylcarboxy].

"Aryl" refers to aromatic groups which have at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl (also known as heteroaryl groups) and biaryl groups, all of which may be optionally substituted. Carbocyclic aryl groups are generally preferred in the compounds of the present invention, where phenyl and naphthyl groups are preferred carbocyclic aryl groups.

"Aralkyl" refers to an alkylene group wherein one of the points of attachment is to an aryl group. An example of an aralkyl group is the benzyl group (Bn) [$\text{C}_6\text{H}_5\text{CH}_2-$, a C_7 aralkyl group].

"Cycloalkyl" refers to a ring, which may be saturated or unsaturated and monocyclic, bicyclic, or tricyclic formed entirely from carbon atoms. An example of a cycloalkyl group is the cyclopentenyl group (C_5H_7-), which is a five carbon (C_5) unsaturated cycloalkyl group.

"Carbocyclic" refers to a ring which may be either an aryl ring or a cycloalkyl ring, both as defined above.

"Carbocyclic aryl" refers to aromatic groups wherein the atoms which form the aromatic ring are carbon atoms. Carbocyclic aryl groups include monocyclic carbocyclic aryl groups such as phenyl, and bicyclic carbocyclic aryl groups such as naphthyl, all of which may be optionally substituted.

"Heteroatom" refers to a non-carbon atom, where boron, nitrogen, oxygen, sulfur and phosphorus are preferred heteroatoms, with nitrogen, oxygen and sulfur being particularly preferred heteroatoms in the compounds of the present invention.

"Heteroaryl" refers to aryl groups having from 1 to 9 carbon atoms and the remainder of the atoms are heteroatoms, and includes those heterocyclic systems described in "Handbook of Chemistry

and Physics," 49th edition, 1968, R.C. Weast, editor; The Chemical Rubber Co., Cleveland, OH. See particularly Section C, Rules for Naming Organic Compounds, B. Fundamental Heterocyclic Systems. Suitable heteroaryls include furanyl, thienyl, pyridyl, pyrrolyl, pyrimidyl, pyrazinyl, imidazolyl, and the like.

"Hydroxyalkyl" refers to a branched or unbranched hydrocarbon fragment bearing an hydroxy (-OH) group. Examples include hydroxymethyl (-CH₂OH, a C₁hydroxyalkyl) and 1-hydroxyethyl (-CHOHCH₃, a C₂hydroxyalkyl).

"Thioalkyl" refers to a sulfur atom substituted by an alkyl group, for example thiomethyl (CH₃S-, a C₁thioalkyl).

"Modulating" in connection with the activity of an ion channel means that the activity of the ion channel may be either increased or decreased in response to administration of a compound or composition or method of the present invention. Thus, the ion channel may be activated, so as to transport more ions, or may be blocked, so that fewer or no ions are transported by the channel.

"Pharmaceutically acceptable carriers" for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remingtons Pharmaceutical Sciences, Mack Publishing Co. (A.R. Gennaro edit. 1985). For example, sterile saline and phosphate-buffered saline at physiological pH may be used. Preservatives, stabilizers, dyes and even flavoring agents may be provided in the pharmaceutical composition. For example, sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid may be added as preservatives. Id. at 1449. In addition, antioxidants and suspending agents may be used. Id.

"Pharmaceutically acceptable salt" refers to salts of the compounds of the present invention derived from the combination of such compounds and an organic or inorganic acid (acid addition salts) or an organic or inorganic base (base addition salts). The compounds of the present invention may be used in either the free base or salt forms, with both forms being considered as being within the scope of the present invention.

The "therapeutically effective amount" of a compound of the present invention will depend on the route of administration, the type of warm-blooded animal being treated, and the physical characteristics of the specific warm-blooded animal under consideration. These factors and their relationship to determining this amount are well known to skilled practitioners in the medical arts. This amount and the method of administration can be tailored to achieve optimal efficacy but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

Compositions described herein as "containing a compound of the present invention" encompass compositions that may contain more than one compound of the present invention formula.

The synthetic procedures described herein, especially when taken with the general knowledge in the art, provide sufficient guidance to perform the synthesis, isolation, and purification of the compounds of the present invention.

The following examples are offered by way of illustration and not by way of limitation. Unless otherwise specified, starting materials and reagents may be obtained from well-known commercial supply houses, e.g., Sigma-Aldrich Fine Chemicals (St. Louis, Missouri), and are of standard grade and purity; or may be obtained by procedures described in the art or adapted therefrom, where suitable procedures may be identified through the Chemical Abstracts and Indices therefor, as developed and published by the American Chemical Society.

Outline of Some General Reaction Processes of the Invention

The aminocyclohexyl ether compounds of the present invention contain ether and amino functional groups disposed in a 1,2 arrangement on a cyclohexane ring. Accordingly, the ether and amino functional groups may be disposed in either a *cis* or *trans* relationship, relative to one another and the plane of the cyclohexane ring. The present invention provides synthetic processes whereby compounds of formula (9) with *trans*-(1*R*,2*R*) configuration for the ether and amino functional groups may be prepared in stereoisomerically substantially pure form. Compound of formula (18) is an example represented by formula (9). The present invention also provides synthetic processes whereby compounds of formula (20) with *trans*-(1*S*,2*S*) configuration for the ether and amino functional groups may be prepared in stereoisomerically substantially pure form. Compound of formula (22) is an example represented by formula (20). The present invention further provides synthetic processes whereby compounds of formulae (4), (5), (7) and (19) may be synthesized in stereoisomerically substantially pure forms. Compounds (11) and (13) are examples of formula (4). Compounds (10) and (12) are examples of formula (5). Compound (16) is an example of formula (7). Compound (21) is an example of formula (19). The aminocyclohexyl ether compounds of the present invention may be used for medical applications, including, for example, cardiac arrhythmia, such as atrial arrhythmia and ventricular arrhythmia.

As outlined in Scheme 1, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (9) may be carried out by following a process starting from a racemic mixture of meso-*cis*-1,2-cyclohexandiol (1). Compound (1) is commercially available (e.g.

Sigma-Aldrich, St. Louis, Missouri) or can be readily synthesized by published methods (e.g. J.E. Taylor et al., *Org. Process Res. & Dev.*, 1998, 2, 147; *Organic Syntheses*, CV6, 342).

In a first step, one of the hydroxy groups of compound (1) is converted under suitable conditions into an activated form as represented by the racemic mixture comprises of formulae (2) and (3). An "activated form" as used herein means that the hydroxy group is converted into a good leaving group ($-O-J$) which on reaction with an appropriate nucleophile will result in a substitution product with inversion of the stereochemical configuration. The leaving group may be any suitable leaving group on reaction with a nucleophilic reactant with inversion of stereochemical configuration known in the art, including but not limited to compounds disclosed in M.B. Smith and J. March in "March's Advanced Organic Chemistry", Fifth edition, Chapter 10, John Wiley & Sons, Inc., New York, NY. (2001). Specific examples of such leaving groups include a mesylate ($MsO-$) group, a tosylate group ($TsO-$), a 2-bromophenylsulfonate group, a 4-bromophenylsulfonate group or a nosylate ($NsO-$) group. The hydroxy group may also be converted into other suitable leaving groups according to procedures well known in the art, using any suitable activating agent, including but not limited to those disclosed in M.B. Smith and J. March in "March's Advanced Organic Chemistry", Fifth edition, Chapter 10, John Wiley & Sons, Inc., New York, NY. (2001). In a typical reaction for the formation of a tosylate, compound (1) is treated with a controlled amount of hydroxy activating reagent such as tosyl chloride ($TsCl$) in the presence of a base, such as pyridine or triethylamine. The reaction may be monitored and is generally satisfactorily conducted at about $0^{\circ}C$, but conditions may be adjusted as required to maximize the yields of the desired product. The addition of other reagents to facilitate the formation of the monotosylates may be advantageously employed (e.g. M.J. Martinelli, et al. "Selective monosulfonylation of internal 1,2-diols catalyzed by di-*n*-butyltin oxide" *Tetrahedron Letters*, 2000, 41, 3773). The racemic mixture comprises of formulae (2) and (3) is then subjected to a resolution process whereby the two optically active isomers are separated into products that are in stereoisomerically substantially pure form such as (4) and (5), wherein G and G_1 are independently selected from hydrogen, C_1-C_8 acyl, or any other suitable functional groups that are introduced as part of the resolution process necessary for the separation of the two isomers. In some situations it may be adequate that the resolution process produces compounds of (4) and (5) of sufficient enrichment in their optical purity for application in the subsequent steps of the synthetic process. Methods for resolution of racemic mixtures are well known in the art (e.g. E.L. Eliel and S.H. Wilen, in *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; Chapter 7, and references cited therein). Suitable processes such as enzymatic resolution (e.g. lipase mediated) and

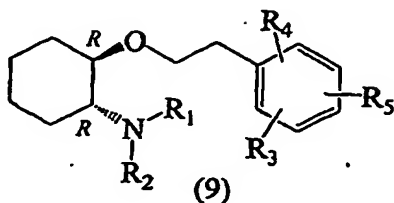
chromatographic separation (e.g. HPLC with chiral stationary phase and/or with simulated moving bed technology) are some of the examples that may be applied.

For compound of formula (4) when G is hydrogen, (4) is the same as compound (2) and in a separate reaction step, alkylation of the free hydroxy group in compound (4) to form compound (7) is carried out under appropriate conditions with compound (6), where $-O-Q$ represents a good leaving group on reaction with a hydroxy function with retention of the stereochemical configuration of the hydroxy function in the formation of an ether compound. The leaving group may be any suitable leaving group known in the art, including but not limited to compounds disclosed in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991). Specific examples of $-O-Q$ groups include trichloroacetimidate. For some compound (6), it may be necessary to introduce appropriate protection groups prior to this step being performed. Suitable protecting groups are set forth in, for example, Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991). For compound of formula (4) when G is not hydrogen, suitable methods are used to convert (4) to compound (2). For example when G is a C_2 acyl function, a mild base-catalyzed methanolysis (G. Zemplen et al., Ber., 1936, 69, 1827) may be used to transform (4) to (2). The latter can then undergo the same reaction with (6) to produce (7) as described above.

In a separate step, the resulted compound (7) is treated under suitable conditions with an amino compound of formula (8) to form compound (9) as the product. The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (9) at a suitable rate. An excess of the amino compound (8) may be used to maximally convert compound (7) to the product (9). The reaction may be performed in the presence of a base that can facilitate the formation of the product. Generally the base is non-nucleophilic in chemical reactivity. When the reaction has proceeded to substantial completion, the product is recovered from the reaction mixture by conventional organic chemistry techniques, and is purified accordingly. Protective groups may be removed at the appropriate stage of the reaction sequence. Suitable methods are set forth in, for example, Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991).

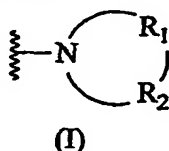
The reaction sequence described above (Scheme 1) generates the compound of formula (9) as the free base. The free base may be converted, if desired, to the monohydrochloride salt by known methodologies, or alternatively, if desired, to other acid addition salts by reaction with an inorganic or organic acid under appropriate conditions. Acid addition salts can also be prepared metathetically by reaction of one acid addition salt with an acid that is stronger than that giving rise to the initial salt.

In one aspect, the present invention provides a process for the preparation of a stereoisomerically substantially pure compound of formula (9):



wherein, independently at each occurrence, R_1 and R_2 are independently selected from hydrogen, C_1 - C_8 alkyl, C_3 - C_8 alkoxyalkyl, C_1 - C_8 hydroxyalkyl, and C_7 - C_{12} aralkyl; or

R_1 and R_2 , when taken together with the nitrogen atom to which they are directly attached in formula (9), form a ring denoted by formula (I):



wherein the ring of formula (I) is formed from the nitrogen as shown as well as three to nine additional ring atoms independently selected from carbon, nitrogen, oxygen, and sulfur; where any two adjacent ring atoms may be joined together by single or double bonds, and where any one or more of the additional carbon ring atoms may be substituted with one or two substituents selected from hydrogen, hydroxy, C_1 - C_3 hydroxyalkyl, oxo, C_2 - C_4 acyl, C_1 - C_3 alkyl, C_2 - C_4 alkylcarboxy, C_1 - C_3 alkoxy, C_1 - C_{20} alkanoyloxy, or may be substituted to form a spiro five- or six-membered heterocyclic ring containing one or two heteroatoms selected from oxygen and sulfur; and any two adjacent additional carbon ring atoms may be fused to a C_3 - C_8 carbocyclic ring, and any one or more of the additional nitrogen ring atoms may be substituted with substituents selected from hydrogen, C_1 - C_6 alkyl, C_2 - C_4 acyl, C_2 - C_4 hydroxyalkyl and C_3 - C_8 alkoxyalkyl; or

R_1 and R_2 , when taken together with the nitrogen atom to which they are directly attached in formula (I), may form a bicyclic ring system selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, and 3-azabicyclo[3.2.0]heptan-3-yl; and

R_3 , R_4 and R_5 are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, cyano, sulfamyl, trifluoromethyl, C_2 - C_7 alkanoyloxy, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_7 alkoxycarbonyl, C_1 - C_6 thioalkyl, aryl and $N(R_6, R_7)$ where R_6 and R_7 are independently selected from hydrogen, acetyl, methanesulfonyl, and C_1 - C_6 alkyl;

comprising the steps of starting with a compound of formula (1), and following a reaction sequence as outlined in Scheme 1 under suitable conditions, wherein

G and G₁ are independently selected from hydrogen, C₁-C₈acyl, or any other suitable functional groups that are introduced as part of the resolution process necessary for the separation of the two isomers;

-O-Q represents a good leaving group on reaction with a hydroxy function with retention of the stereochemical configuration of the hydroxy function in the formation of an ether compound, including but not limited to, those disclosed in "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991); and

-O-J represents a good leaving group on reaction with a nucleophilic reactant with inversion of the stereochemical configuration, including, but not limited to, those disclosed in "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991), as shown in Scheme 1 and all the formulae and symbols are as described above.

In another aspect, the present invention provides a process for the preparation of a stereoisomerically substantially pure compound of formula (18), comprising the steps under suitable conditions as shown in Scheme 2, wherein all the formulae and symbols are as described above. As outlined in Scheme 2, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out by starting with the monotosylation of *cis*-1,2-cyclohexandiol (1) with TsCl in the presence of Bu₂SnO and triethylamine under suitable conditions (M.J. Martinelli, et al. "Selective monosulfonylation of internal 1,2-diols catalyzed by di-*n*-butyltin oxide" Tetrahedron Letters, 2000, 41, 3773). Initial non-optimized yields of 80-90% have been achieved, and further optimization is being pursued. The resulting racemic mixture of hydroxytosylates comprises compounds (11) and (10) is subjected to a lipase-mediated resolution process under suitable conditions such as treatment of the racemates (11) and (10) with vinyl acetate (14) in the presence of a lipase derived from *Pseudomonas sp.* (N. Boaz et al., Tetra. Asymmetry, 1994, 5, 153) to provide compound (11) and (12). In a separate step, the stereoisomerically substantially pure compound of formula (11) obtained from the resolution process is alkylated under appropriate conditions by treatment with the trichloroacetimidate (15) to form compound (16). Initial non-optimized yields of 60-70% have been achieved, and further optimization is being pursued. The trichloroacetimidate (15) is readily prepared from the corresponding alcohol, 3,4-dimethoxyphenethyl alcohol which is commercially available (e.g. Sigma-Aldrich, St. Louis, Missouri), by treatment with trichloroacetonitrile. The alkylation of compound (11) by trichloroacetimidate (15) may be carried out in the presence of a Lewis acid such as HBF₄.

In another separate step, the tosylate group of formula (16) is displaced by an amino compound such as 3*R*-pyrrolidinol (17) with inversion of configuration. 3*R*-pyrrolidinol (17) is commercially available (e.g. Sigma-Aldrich, St. Louis, Missouri) or may be prepared according to published procedure (e.g. Chem.Ber./Recueil 1997, 130, 385-397). The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (18) at a suitable rate. An excess of the amino compound (17) may be used to maximally convert compound (16) to the product (18). The reaction may be performed in the presence of a base that can facilitate the formation of the product. Generally the additional base is non-nucleophilic in chemical reactivity. When the reaction has proceeded to substantial completion, the desired product is recovered from the reaction mixture by conventional organic chemistry techniques, and is purified accordingly. Initial non-optimized yields of approximately 40% have been achieved, and further optimization is being pursued.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in Scheme 3, comprising the steps under suitable conditions as shown in Scheme 3, wherein all the formulae and symbols are as described above. As outlined in Scheme 3, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out by starting with the monotosylation of the *cis*-1,2-cyclohexandiol (1) with TsCl in the presence of Bu₂SnO and triethylamine under suitable conditions (M.J. Martinelli, et al. "Selective monosulfonylation of internal 1,2-diols catalyzed by di-*n*-butyltin oxide" Tetrahedron Letters, 2000, 41, 3773). The resulting racemic mixture of hydroxytosylates comprises of compounds (11) and (10) is subjected to a lipase-mediated resolution process under suitable conditions such as treatment of the racemates (11) and (10) with vinyl acetate (14) in the presence of a lipase derived from *Pseudomonas* sp. (N. Boaz et al., Tetra. Asymmetry, 1994, 5, 153) to provide compound (13) and (10).

In a separate step, the stereoisomerically substantially pure compound of formula (13) obtained from the resolution process is subjected to a mild base-catalyzed methanolysis (G. Zemplén et al., Ber., 1936, 69, 1827) to form compound (11). The latter is alkylated under appropriate conditions by treatment with the trichloroacetimidate (15) to form compound (16). The trichloroacetimidate (15) is readily prepared from the corresponding alcohol, 3,4-dimethoxyphenethyl alcohol which is commercially available (e.g. Sigma-Aldrich, St. Louis, Missouri), by treatment with trichloroacetonitrile. The alkylation of compound (14) by trichloroacetimidate (15) may be carried out in the presence of a Lewis acid such as HBF₄.

In another separate step, the tosylate group of formula (16) is displaced by an amino compound such as 3*R*-pyrrolidinol (17) with inversion of configuration. 3*R*-pyrrolidinol (17) is commercially available (e.g. Sigma-Aldrich, St. Louis, Missouri) or may be prepared according to published procedure (e.g. Chem.Ber./Recueil 1997, 130, 385-397). The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (18) at a suitable rate. An excess of the amino compound (17) may be used to maximally convert compound (16) to the product (18). The reaction may be performed in the presence of a base that can facilitate the formation of the product. Generally the additional base is non-nucleophilic in chemical reactivity. When the reaction has proceeded to substantial completion, the desired product is recovered from the reaction mixture by conventional organic chemistry techniques, and is purified accordingly.

In another aspect, the present invention provides a process for the preparation of a stereoisomerically substantially pure compound of formula (18), comprising the steps under suitable conditions as shown in Scheme 4, wherein all the formulae and symbols are as described above. As outlined in Scheme 4, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out by starting with the monotosylation of the *cis*-1,2-cyclohexandiol (1) with TsCl in the presence of Bu₂SnO and triethylamine under suitable conditions (M.J. Martinelli, et al. "Selective monosulfonylation of internal 1,2-diols catalyzed by di-*n*-butyltin oxide" Tetrahedron Letters, 2000, 41, 3773). The resulting racemic mixture of hydroxytosylates comprises of compounds (11) and (10) is subjected to a chromatographic resolution process under suitable conditions such as HPLC with an appropriate chiral stationary phase and simulated moving bed technology to provide compounds (11) and (10) in stereoisomerically substantially pure form.

In a separate step, the stereoisomerically substantially pure compound of formula (11) obtained from the resolution process is alkylated under appropriate conditions by treatment with the trichloroacetimidate (15) to form compound (16). The trichloroacetimidate (15) is readily prepared from the corresponding alcohol, 3,4-dimethoxyphenethyl alcohol which is commercially available (e.g. Sigma-Aldrich, St. Louis, Missouri), by treatment with trichloroacetonitrile. The alkylation of compound (11) by trichloroacetimidate (15) may be carried out in the presence of a Lewis acid such as HBF₄.

In another separate step, the tosylate group of formula (16) is displaced by an amino compound such as 3*R*-pyrrolidinol (17) with inversion of configuration. 3*R*-pyrrolidinol (17) is commercially available (e.g. Sigma-Aldrich, St. Louis, Missouri) or may be prepared according to published procedure (e.g. Chem.Ber./Recueil 1997, 130, 385-397). The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (18) at a suitable rate. An

excess of the amino compound (17) may be used to maximally convert compound (16) to the product (18). The reaction may be performed in the presence of a base that can facilitate the formation of the product. Generally the additional base is non-nucleophilic in chemical reactivity. When the reaction has proceeded to substantial completion, the desired product is recovered from the reaction mixture by conventional organic chemistry techniques, and is purified accordingly.

The reaction sequences described above (Scheme 2, Scheme 3 and Scheme 4) in general generate the compound of formula (18) as the free base. The free base may be converted, if desired, to the monohydrochloride salt by known methodologies, or alternatively, to other acid addition salts by reaction with an inorganic or organic acid under appropriate conditions. Acid addition salts can also be prepared metathetically by reaction of one acid addition salt with an acid that is stronger than that giving rise to the initial salt.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (9) may be carried out under suitable conditions by a process as outlined in Scheme 5, comprising the steps of starting with a racemic mixture comprising of formulae (2) and (3) and following a reaction sequence analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in Scheme 6, comprising the steps of starting with a racemic mixture comprising of formulae (11) and (10) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2 wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in Scheme 7, comprising the steps of starting with a racemic mixture comprising of formulae (11) and (10) and following a reaction sequence analogous to the applicable portion that is described in Scheme 3, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in Scheme 8, comprising the steps of starting with a racemic mixture comprising of formulae (11) and (10) and following a reaction sequence analogous to the applicable portion that is described in Scheme 4, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohex ether compound of formula (9) may be carried out under suitable conditions by a process as outlined Scheme 9, comprising the steps of starting with a compound of formula (4) where G is hydrogen and following a reaction sequence analogous to the applicable portion that is described in Scheme 1, where all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohex ether compound of formula (9) may be carried out under suitable conditions by a process as outlined Scheme 10, comprising the steps of starting with a compound of formula (4) where G is not hydrogen and following a reaction sequence analogous to the applicable portion that is described in Scheme 1, where all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohex ether compound of formula (18) may be carried out under suitable conditions by a process as outlined Scheme 11, comprising the steps of starting with a compound of formula (11) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohex ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in Scheme 12, comprising the steps of starting with a compound of formula (13) and following a reaction sequence analogous to the applicable portion that is described in Scheme 3, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohex ether compound of formula (9) may be carried out under suitable conditions by a process as outlined in Scheme 13, comprising the steps of starting with a compound of formula (7) and following a reaction sequence analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohex ether compound of formula (18) may be carried out under suitable conditions by a process as outlined in Scheme 14, comprising the steps of starting with a compound of formula (16) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (7) may be carried out under suitable conditions by a process as outlined in Scheme 15, comprising the steps of starting with compound of formula (1) and following a reaction sequence analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (7) may be carried out under suitable conditions by a process as outlined in Scheme 16, comprising the steps of starting with compound of formula (1) and following a reaction sequence analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (16) may be carried out under suitable conditions by a process as outlined in Scheme 17, comprising the steps of starting with compound of formula (1) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (16) may be carried out under suitable conditions by a process as outlined in Scheme 18, comprising the steps of starting with compound of formula (1) and following a reaction sequence analogous to the applicable portion that is described in Scheme 3, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (16) may be carried out under suitable conditions by a process as outlined in Scheme 19, comprising the steps of starting with compound of formula (1) and following a reaction sequence analogous to the applicable portion that is described in Scheme 4, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of stereoisomerically substantially pure compounds of formulae (4) and (5) may be carried out under suitable conditions by a process as outlined in Scheme 20, comprising the steps of starting with compound of formula (1) and following a reaction sequence analogous to the applicable portion that is described in Scheme 1, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of stereoisomerically substantially pure compounds of formulae (11) and (12) may be carried out under suitable conditions by a process as outlined in Scheme 21,

comprising the steps of starting with compound of formula (1) and following a reaction sequence analogous to the applicable portion that is described in Scheme 2, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of stereoisomerically substantially pure compounds of formula (13) and (10) may be carried out under suitable conditions by a process as outlined in Scheme 22 comprising the steps of starting with compound of formula (1) and following a reaction sequence analogous to the applicable portion that is described in Scheme 3, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of stereoisomerically substantially pure compounds of formula (11) and (10) may be carried out under suitable conditions by a process as outlined in Scheme 23, comprising the steps of starting with compound of formula (1) and following a reaction sequence analogous to the applicable portion that is described in Scheme 4, wherein all the formulae and symbols are as described above.

In another aspect, the present invention further provides synthetic processes whereby compounds of formula (20) with *trans*-(1*S*,2*S*) configuration for the ether and amino functional groups may be prepared in stereoisomerically substantially pure form. As outlined in Scheme 24, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out by following a process starting from a racemic mixture of meso-*cis*-1,2-cyclohexandiol (1). Compound (1) is commercially available (e.g. Sigma-Aldrich, St. Louis, Missouri) or can be readily synthesized by published methods (e.g. J.E. Taylor et al., *Org. Process Res. & Dev.*, 1998, 2, 147; *Organic Syntheses*, CV6, 342).

In a first step, one of the hydroxy groups of compound (1) is converted under suitable conditions into an activated form as represented by the racemic mixture comprises of formulae (2) and (3). An "activated form" as used herein means that the hydroxy group is converted into a good leaving group (-O-J) which on reaction with an appropriate nucleophile will result in a substitution product with inversion of the stereochemical configuration. The leaving group may be any suitable leaving group on reaction with a nucleophilic reactant with inversion of stereochemical configuration known in the art, including but not limited to compounds disclosed in M.B. Smith and J. March in "March's Advanced Organic Chemistry", Fifth edition, Chapter 10, John Wiley & Sons, Inc., New York, NY. (2001). Specific examples of such leaving groups include a mesylate (MsO-) group, a tosylate group (TsO-), a 2-bromophenylsulfonate group, a 4-bromophenylsulfonate group or a nosylate (NsO-) group. The hydroxy group may also be converted into other suitable leaving groups according to procedures well known in the

art, using any suitable activating agent, including but not limited to those disclosed in M.B. Smith and J. March in "March's Advanced Organic Chemistry", Fifth edition, Chapter 10, John Wiley & Sons, Inc. New York, NY. (2001). In a typical reaction for the formation of a tosylate, compound (1) is treated with a controlled amount of hydroxy activating reagent such as tosyl chloride (TsCl) in the presence of a base such as pyridine or triethylamine. The reaction may be monitored and is generally satisfactorily conducted at about 0°C, but conditions may be adjusted as required to maximize the yields of the desired product. The addition of other reagents to facilitate the formation of the monotosylates may be advantageously employed (e.g. M.J. Martinelli, et al. "Selective monosulfonylation of internal 1,2-diols catalyzed by di-*n*-butyltin oxide" Tetrahedron Letters, 2000, 41, 3773). The racemic mixture comprises of formulae (2) and (3) is then subjected to a resolution process whereby the two optically active isomers are separated into products that are in stereoisomerically substantially pure form such as (4) and (5), wherein G and G₁ are independently selected from hydrogen, C₁-C₃acyl, or any other suitable functional groups that are introduced as part of the resolution process necessary for the separation of the two isomers. In some situations it may be adequate that the resolution process produces compounds of (4) and (5) of sufficient enrichment in their optical purity for application in the subsequent steps of the synthetic process. Methods for resolution of racemic mixtures are well known in the art (e.g. E.L. Eliel and S.H. Wilen, in *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; Chapter 7, and references cited therein). Suitable processes such as enzymatic resolution (e.g. lipase mediated) and chromatographic separation (e.g. HPLC with chiral stationary phase and/or with simulated moving bed technology) are some of the methods that may be applied.

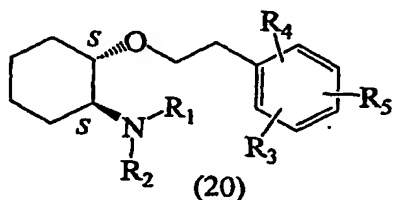
For compound of formula (5) when G₁ is hydrogen, (5) is the same as compound (3) and in a separate reaction step, alkylation of the free hydroxy group in compound (5) to form compound (19) is carried out under appropriate conditions with compound (6), where -O-Q represents a good leaving group on reaction with a hydroxy function with retention of the stereochemical configuration of the hydroxy function in the formation of an ether compound. The leaving group may be any suitable leaving group known in the art, including but not limited to compounds disclosed in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991). Trichloroacetimidate is one example for the -O-Q function. For some compound (6), it may be necessary to introduce appropriate protection groups prior to this step being performed. Suitable protecting groups are set forth in, for example, Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991). For compound of formula (5) when G₁ is not hydrogen, suitable methods are used to convert (5) to compound (3). For example when G₁ is a C₂ acyl function, a mild base-catalyzed methanolysis (G. Zemplen et al.,

Ber., 1936, 69, 1827) may be used to transform (5) to (3). The latter can then undergo the same reaction with (6) to produce (19) as described above.

In a separate step, the resulted compound (19) is treated under suitable conditions with an amino compound of formula (8) to form compound (20) as the product. The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (20) at a suitable rate. An excess of the amino compound (8) may be used to maximally convert compound (19) to the product (20). The reaction may be performed in the presence of a base that can facilitate the formation of the product. Generally the base is non-nucleophilic in chemical reactivity. When the reaction has proceeded to substantial completion, the product is recovered from the reaction mixture by conventional organic chemistry techniques, and is purified accordingly. Protective groups may be removed at the appropriate stage of the reaction sequence. Suitable methods are set forth in, for example Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991).

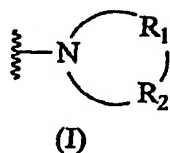
The reaction sequence described above (Scheme 24) generates the compound of formula (20) as the free base. The free base may be converted, if desired, to the monohydrochloride salt by known methodologies, or alternatively, if desired, to other acid addition salts by reaction with an inorganic or organic acid under appropriate conditions. Acid addition salts can also be prepared metathetically by reaction of one acid addition salt with an acid that is stronger than that giving rise to the initial salt.

In one aspect, the present invention provides a process for the preparation of a stereoisomerically substantially pure compound of formula (20):



wherein, independently at each occurrence, R_1 and R_2 are independently selected from hydrogen, C_1 - C_8 alkyl, C_3 - C_8 alkoxyalkyl, C_1 - C_8 hydroxyalkyl, and C_7 - C_{12} aralkyl; or

R_1 and R_2 , when taken together with the nitrogen atom to which they are directly attached in formula (20), form a ring denoted by formula (I):



wherein the ring of formula (I) is formed from the nitrogen as shown as well as three to nine additional ring atoms independently selected from carbon, nitrogen, oxygen, and sulfur; where any two adjacent ring atoms may be joined together by single or double bonds, and where any one or more of the additional carbon ring atoms may be substituted with one or two substituents selected from hydrogen, hydroxyl, C₁-C₃hydroxyalkyl, oxo, C₂-C₄acyl, C₁-C₃alkyl, C₂-C₄alkylcarboxy, C₁-C₃alkoxy, C₁-C₂₀alkanoyloxy, may be substituted to form a spiro five- or six-membered heterocyclic ring containing one or two heteroatoms selected from oxygen and sulfur; and any two adjacent additional carbon ring atoms may be fused to a C₃-C₈carbocyclic ring, and any one or more of the additional nitrogen ring atoms may be substituted with substituents selected from hydrogen, C₁-C₆alkyl, C₂-C₄acyl, C₂-C₄hydroxyalkyl and C₃-C₈alkoxyalkyl; or

R₁ and R₂, when taken together with the nitrogen atom to which they are directly attached in formula (I), may form a bicyclic ring system selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, and 3-azabicyclo[3.2.0]heptan-3-yl; and

R₃, R₄ and R₅ are independently selected from bromine, chlorine, fluorine, carboxy, hydroxyl, hydroxy, hydroxymethyl, methanesulfonamido, nitro, cyano, sulfamyl, trifluoromethyl, C₂-C₇alkanoyloxy, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₇alkoxycarbonyl, C₁-C₆thioalkyl, aryl and N(R₆,R₇) where R₆ and R₇ are independently selected from hydrogen, acetyl, methanesulfonyl, and C₁-C₆alkyl;

comprising the steps of starting with a compound of formula (1), and following a reaction sequence as outlined in Scheme 24 under suitable conditions, wherein

G and G₁ are independently selected from hydrogen, C₁-C₈acyl, or any other suitable functional groups that are introduced as part of the resolution process necessary for the separation of the two isomers;

-O-Q represents a good leaving group on reaction with a hydroxy function with retention of the stereochemical configuration of the hydroxy function in the formation of an ether compound, including but not limited to, those disclosed in "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991); and

-O-J represents a good leaving group on reaction with a nucleophilic reactant with inversion of the stereochemical configuration, including, but not limited to, those disclosed in "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991), as shown in Scheme 24 and all the formulae and symbols are as described above.

In another aspect, the present invention provides a process for the preparation of a stereoisomerically substantially pure compound of formula (22), comprising the steps under suitable

conditions as shown in Scheme 25, wherein all the formulae and symbols are as described above. As outlined in Scheme 25, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out by starting with the monotosylation of *cis*-1,2-cyclohexandiol (1) with TsCl in the presence of Bu₂SnO and triethylamine under suitable conditions (M.J. Martinelli, et al. "Selective monosulfonylation of internal 1,2-diols catalyzed by di-*n*-butyltin oxide Tetrahedron Letters, 2000, 41, 3773). The resulting racemic mixture of hydroxytosylates comprises compounds (11) and (10) is subjected to a lipase-mediated resolution process under suitable conditions such as treatment of the racemates (11) and (10) with vinyl acetate (14) in the presence of a lipase derived from *Pseudomonas sp.* (N. Boaz et al., Tetra. Asymmetry, 1994, 5, 153) to provide compound (10) and (13). In a separate step, the stereoisomerically substantially pure compound of formula (10) obtained from the resolution process is alkylated under appropriate conditions by treatment with the trichloroacetimidate (15) to form compound (21). The trichloroacetimidate (15) is readily prepared from the corresponding alcohol, 3,4-dimethoxyphenethyl alcohol which is commercially available (e.g. Sigma-Aldrich, St. Louis, Missouri), by treatment with trichloroacetonitrile. The alkylation of compound (10) by trichloroacetimidate (15) may be carried out in the presence of a Lewis acid such as HBF₄.

In another separate step, the tosylate group of formula (21) is displaced by an amino compound such as 3*R*-pyrrolidinol (17) with inversion of configuration. 3*R*-pyrrolidinol (17) is commercially available (e.g. Sigma-Aldrich, St. Louis, Missouri) or may be prepared according to published procedure (e.g. Chem.Ber./Recueil 1997, 130, 385-397). The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (22) at a suitable rate. An excess of the amino compound (17) may be used to maximally convert compound (21) to the product (22). The reaction may be performed in the presence of a base that can facilitate the formation of the product. Generally the additional base is non-nucleophilic in chemical reactivity. When the reaction has proceeded to substantial completion, the desired product is recovered from the reaction mixture by conventional organic chemistry techniques, and is purified accordingly.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 26, comprising the steps under suitable conditions as shown in Scheme 26, wherein all the formulae and symbols are as described above. As outlined in Scheme 26, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out by starting with the monotosylation of the *cis*-1,2-cyclohexandiol (1) with TsCl in the presence of Bu₂SnO and triethylamine under suitable conditions (M.J. Martinelli, et al. "Selective

monosulfonylation of internal 1,2-diols catalyzed by di-*n*-butyltin oxide" Tetrahedron Letters, 2000, 41, 3773). The resulting racemic mixture of hydroxytosylates comprises of compounds (11) and (10) is subjected to a lipase-mediated resolution process under suitable conditions such as treatment of the racemates (11) and (10) with vinyl acetate (14) in the presence of a lipase derived from *Pseudomonas sp.* (N. Boaz et al., Tetra. Asymmetry, 1994, 5, 153) to provide compound (12) and (11).

In a separate step, the stereoisomerically substantially pure compound of formula (12) obtained from the resolution process is subjected to a mild base-catalyzed methanolysis (G. Zemplen et al., Ber., 1936, 69, 1827) to form compound (10). The latter is alkylated under appropriate conditions by treatment with the trichloroacetimidate (15) to form compound (21). The trichloroacetimidate (15) is readily prepared from the corresponding alcohol, 3,4-dimethoxyphenethyl alcohol which is commercially available (e.g. Sigma-Aldrich, St. Louis, Missouri), by treatment with trichloroacetonitrile. The alkylation of compound (10) by trichloroacetimidate (15) may be carried out in the presence of a Lewis acid such as HBF₄.

In another separate step, the tosylate group of formula (21) is displaced by an amino compound such as 3*R*-pyrrolidinol (17) with inversion of configuration. 3*R*-pyrrolidinol (17) is commercially available (e.g. Sigma-Aldrich, St. Louis, Missouri) or may be prepared according to published procedure (e.g. Chem.Ber./Recueil 1997, 130, 385-397). The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (22) at a suitable rate. An excess of the amino compound (17) may be used to maximally convert compound (21) to the product (22). The reaction may be performed in the presence of a base that can facilitate the formation of the product. Generally the additional base is non-nucleophilic in chemical reactivity. When the reaction has proceeded to substantial completion, the desired product is recovered from the reaction mixture by conventional organic chemistry techniques, and is purified accordingly.

In another aspect, the present invention provides a process for the preparation of a stereoisomerically substantially pure compound of formula (22), comprising the steps under suitable conditions as shown in Scheme 27, wherein all the formulae and symbols are as described above. As outlined in Scheme 27, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out by starting with the monotosylation of the *cis*-1,2-cyclohexandiol (1) with TsCl in the presence of Bu₂SnO and triethylamine under suitable conditions (M.J. Martinelli, et al. "Selective monosulfonylation of internal 1,2-diols catalyzed by di-*n*-butyltin oxide" Tetrahedron Letters, 2000, 41, 3773). The resulting racemic mixture of hydroxytosylates comprises of compounds (11) and (10) is subjected to a chromatographic resolution process under suitable conditions

such as HPLC with an appropriate chiral stationary phase and simulated moving bed technology to provide compounds (11) and (10) in stereoisomerically substantially pure form.

In a separate step, the stereoisomerically substantially pure compound of formula (10) obtained from the resolution process is alkylated under appropriate conditions by treatment with the trichloroacetimidate (15) to form compound (16). The trichloroacetimidate (15) is readily prepared from the corresponding alcohol, 3,4-dimethoxyphenethyl alcohol which is commercially available (e.g. Sigma-Aldrich, St. Louis, Missouri), by treatment with trichloroacetonitrile. The alkylation of compound (10) by trichloroacetimidate (15) may be carried out in the presence of a Lewis acid such as HBF_4 .

In another separate step, the tosylate group of formula (21) is displaced by an amino compound such as 3*R*-pyrrolidinol (17) with inversion of configuration. 3*R*-pyrrolidinol (17) is commercially available (e.g. Sigma-Aldrich, St. Louis, Missouri) or may be prepared according to published procedure (e.g. Chem.Ber./Recueil 1997, 130, 385-397). The reaction may be carried out with or without a solvent and at an appropriate temperature range that allows the formation of the product (22) at a suitable rate. An excess of the amino compound (17) may be used to maximally convert compound (21) to the product (22). The reaction may be performed in the presence of a base that can facilitate the formation of the product. Generally the additional base is non-nucleophilic in chemical reactivity. When the reaction has proceeded to substantial completion, the desired product is recovered from the reaction mixture by conventional organic chemistry techniques, and is purified accordingly.

The reaction sequences described above (Scheme 25, Scheme 26 and Scheme 27) in general generate the compound of formula (22) as the free base. The free base may be converted, if desired, to the monohydrochloride salt by known methodologies, or alternatively, to other acid addition salts by reaction with an inorganic or organic acid under appropriate conditions. Acid addition salts can also be prepared metathetically by reaction of one acid addition salt with an acid that is stronger than that giving rise to the initial salt.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out under suitable conditions by a process as outlined in Scheme 28, comprising the steps of starting with a racemic mixture comprises of formulae (2) and (3) and following a reaction sequence analogous to the applicable portion that is described in Scheme 24, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 29, comprising the steps of starting with a racemic mixture comprises of formulae (11) and (10)

and following a reaction sequence analogous to the applicable portion that is described in Scheme 25 wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 30, comprising the steps of starting with a racemic mixture comprises of formulae (11) and (10) and following a reaction sequence analogous to the applicable portion that is described in Scheme 26 wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 31, comprising the steps of starting with a racemic mixture comprises of formulae (11) and (10) and following a reaction sequence analogous to the applicable portion that is described in Scheme 27 wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out under suitable conditions by a process as outlined in Scheme 32, comprising the steps of starting with a compound of formula (5) where G_1 is hydrogen and following a reaction sequence analogous to the applicable portion that is described in Scheme 24, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out under suitable conditions by a process as outlined in Scheme 33, comprising the steps of starting with a compound of formula (5) where G_1 is not hydrogen and following a reaction sequence analogous to the applicable portion that is described in Scheme 24, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 34, comprising the steps of starting with a compound of formula (10) and following a reaction sequence analogous to the applicable portion that is described in Scheme 25, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 35, comprising the steps of starting with a compound of formula (12) and following a reaction sequence analogous to the applicable portion that is described in Scheme 26, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (20) may be carried out under suitable conditions by a process as outlined in Scheme 36, comprising the steps of starting with a compound of formula (19) and following a reaction sequence analogous to the applicable portion that is described in Scheme 24, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure *trans* aminocyclohexyl ether compound of formula (22) may be carried out under suitable conditions by a process as outlined in Scheme 37, comprising the steps of starting with a compound of formula (21) and following a reaction sequence analogous to the applicable portion that is described in Scheme 25, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (19) may be carried out under suitable conditions by a process as outlined in Scheme 38, comprising the steps of starting with compound of formula (1) and following a reaction sequence analogous to the applicable portion that is described in Scheme 24, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (19) may be carried out under suitable conditions by a process as outlined in Scheme 39, comprising the steps of starting with compound of formula (1) and following a reaction sequence analogous to the applicable portion that is described in Scheme 24, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (21) may be carried out under suitable conditions by a process as outlined in Scheme 40, comprising the steps of starting with compound of formula (1) and following a reaction sequence analogous to the applicable portion that is described in Scheme 25, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (21) may be carried out under suitable conditions by a process as outlined in Scheme 41, comprising the steps of starting with compound of formula (1) and following a reaction sequence analogous to the applicable portion that is described in Scheme 26, wherein all the formulae and symbols are as described above.

In another aspect, the preparation of a stereoisomerically substantially pure compound of formula (21) may be carried out under suitable conditions by a process as outlined in Scheme 42, comprising the

steps of starting with compound of formula (1) and following a reaction sequence analogous to the applicable portion that is described in Scheme 27, wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (4), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (5), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (6), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above with the proviso that R_3 , R_4 and R_5 cannot all be hydrogen.

In another aspect, the present invention provides a compound of formula (7), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above with the proviso that when R_3 , R_4 and R_5 are all hydrogen then J is not a methanesulfonyl group.

In another aspect, the present invention provides a compound of formula (10), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (11), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (12), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

In another aspect, the present invention provides a compound of formula (13), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

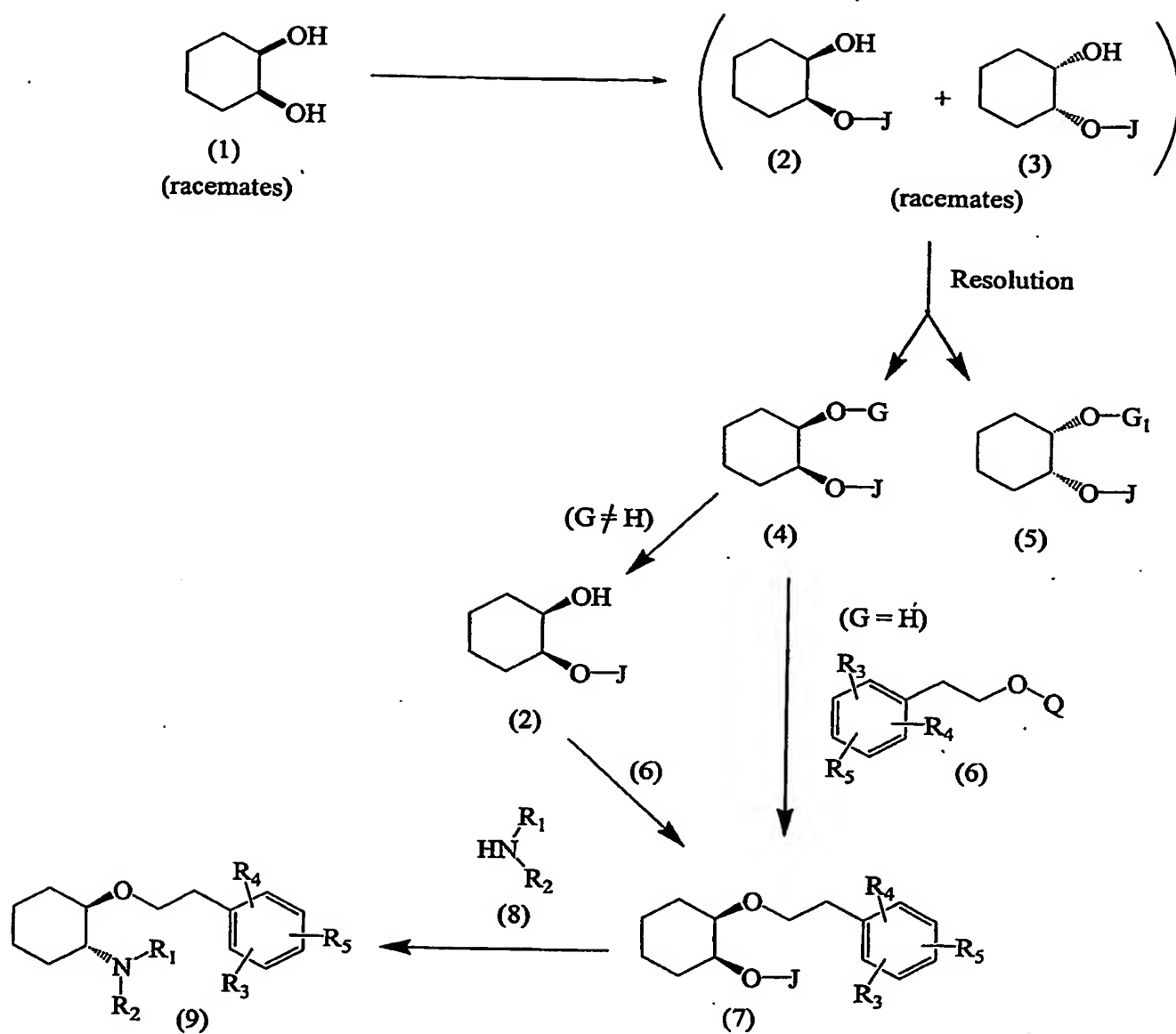
In another aspect, the present invention provides a compound of formula (16), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

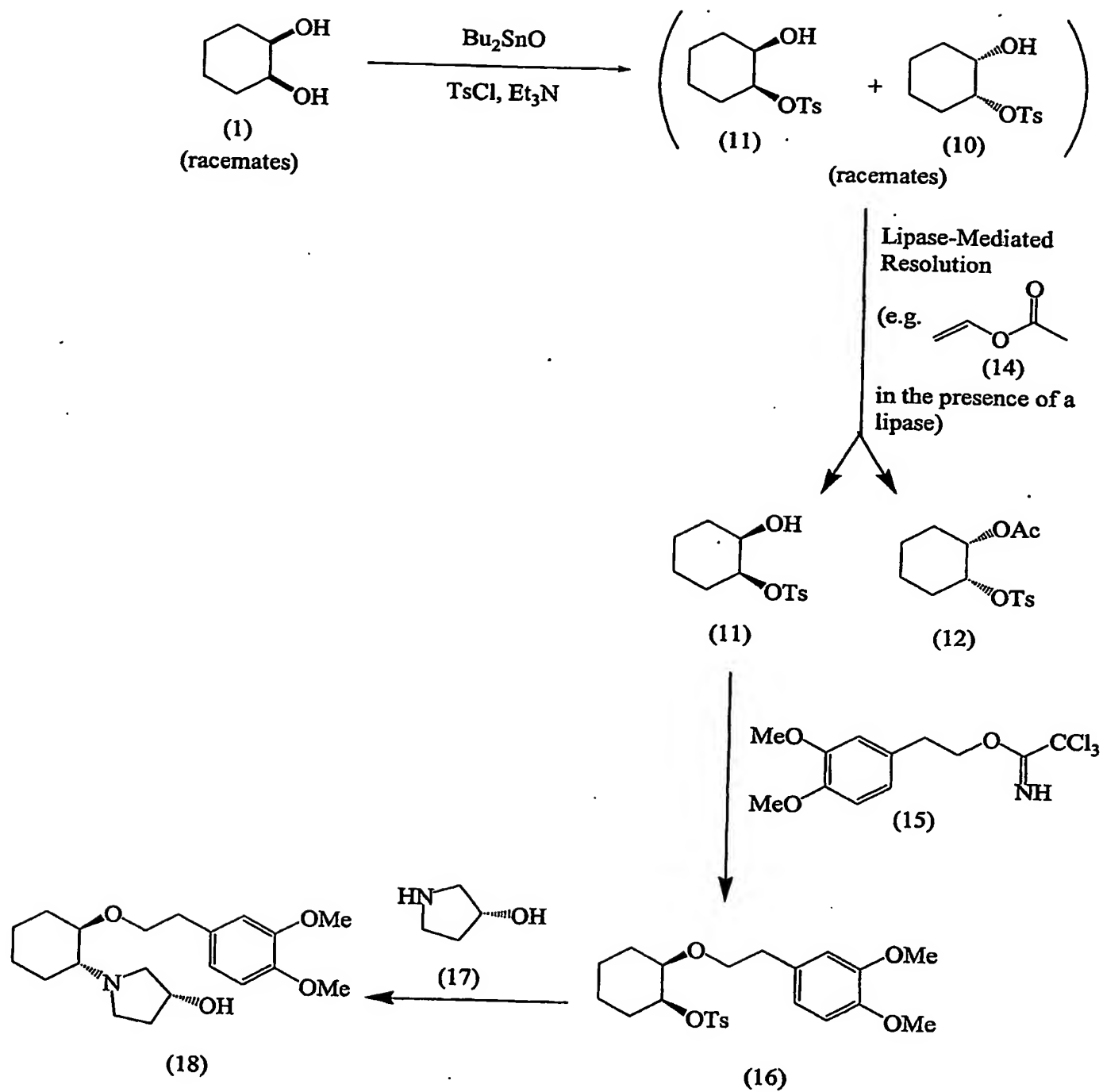
In another aspect, the present invention provides a compound of formula (19), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above with the proviso that when R_3 , R_4 and R_5 are all hydrogen then J is not a methanesulfonyl group.

In another aspect, the present invention provides a compound of formula (21), or a solvate or pharmaceutically acceptable salt thereof; wherein all the formulae and symbols are as described above.

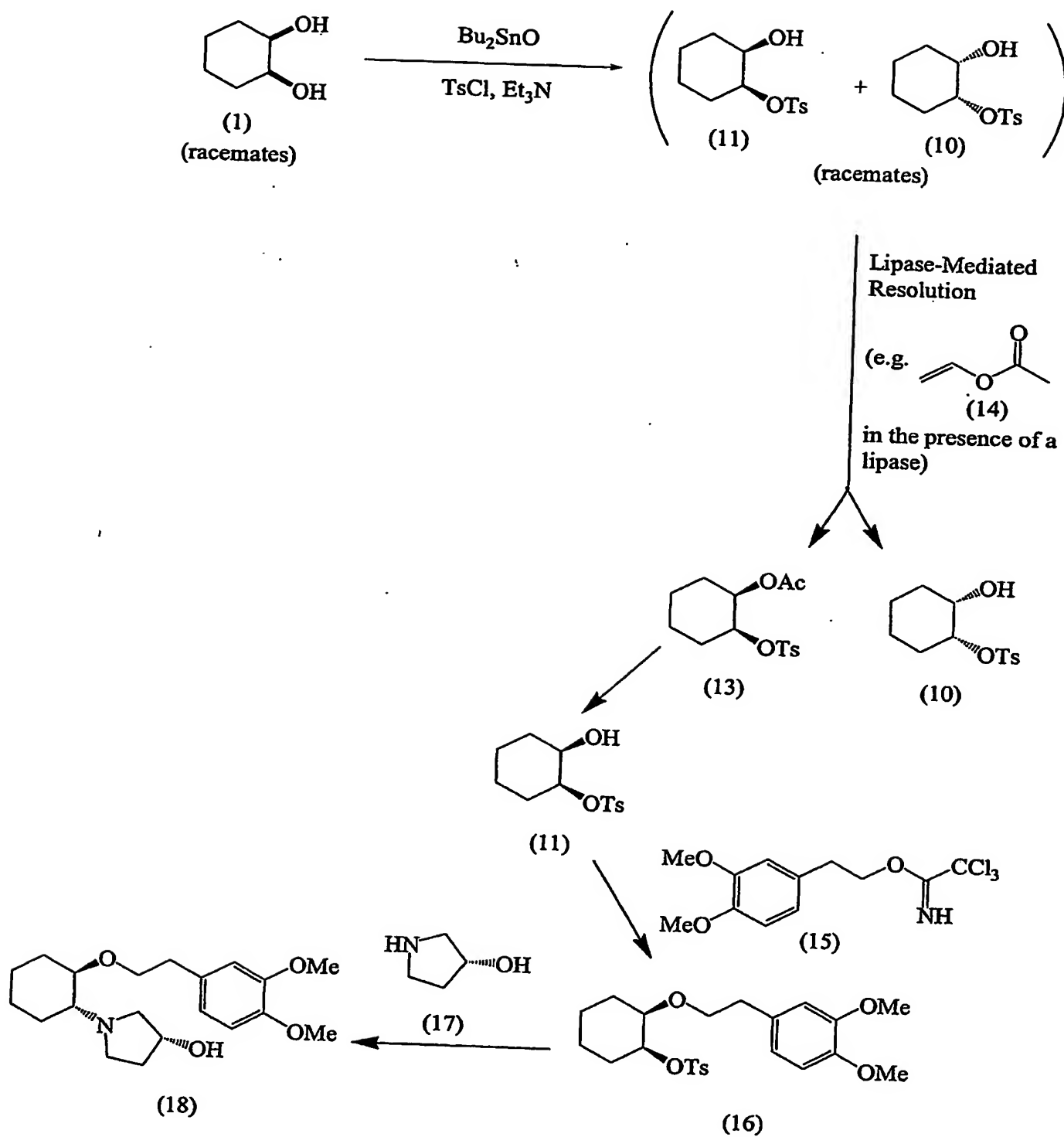
All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual publication, patent, or patent application were specifically and individually indicated to be so incorporated by reference. Although the

foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit and scope of the patent application.

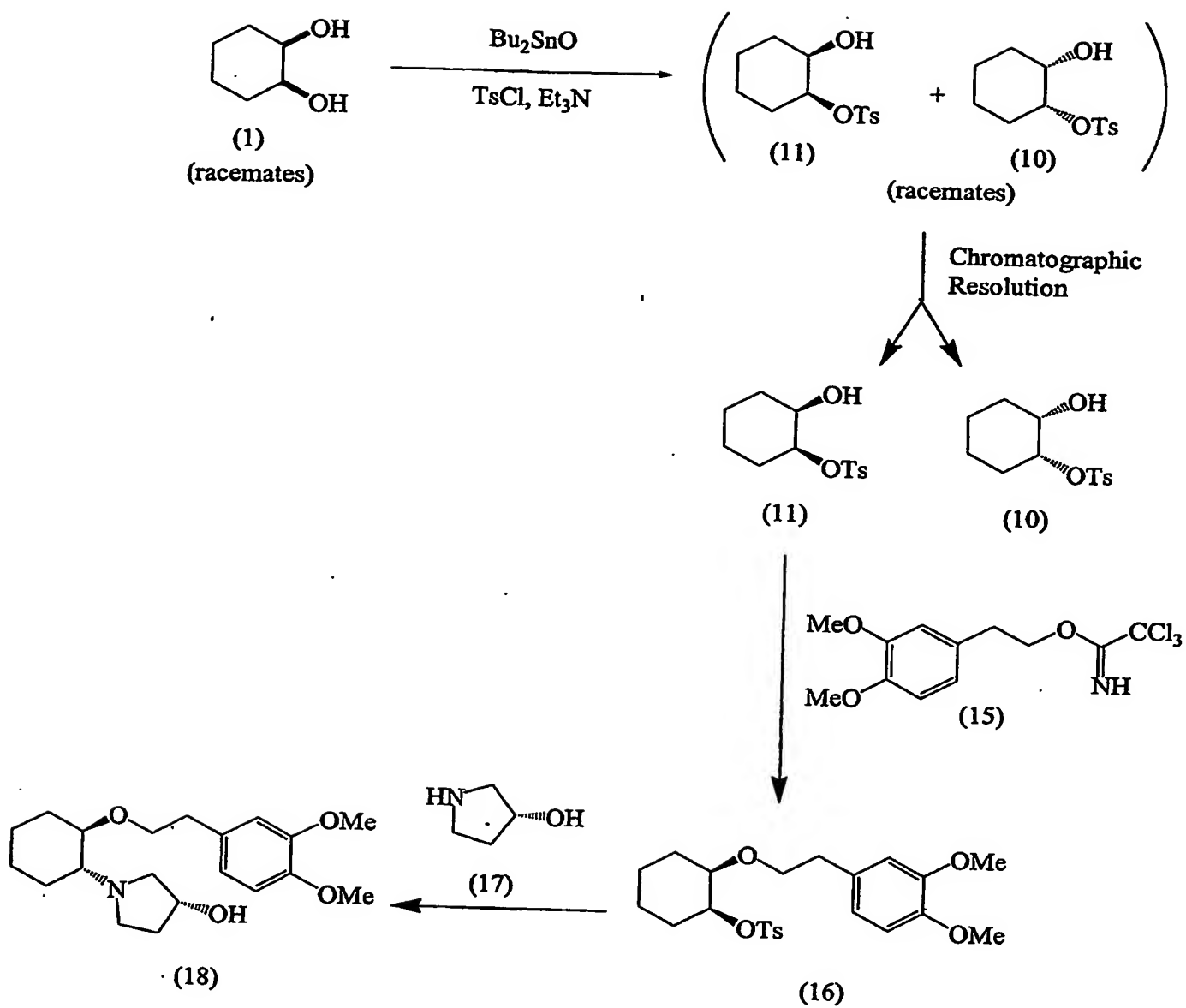
Scheme 1

Scheme 2

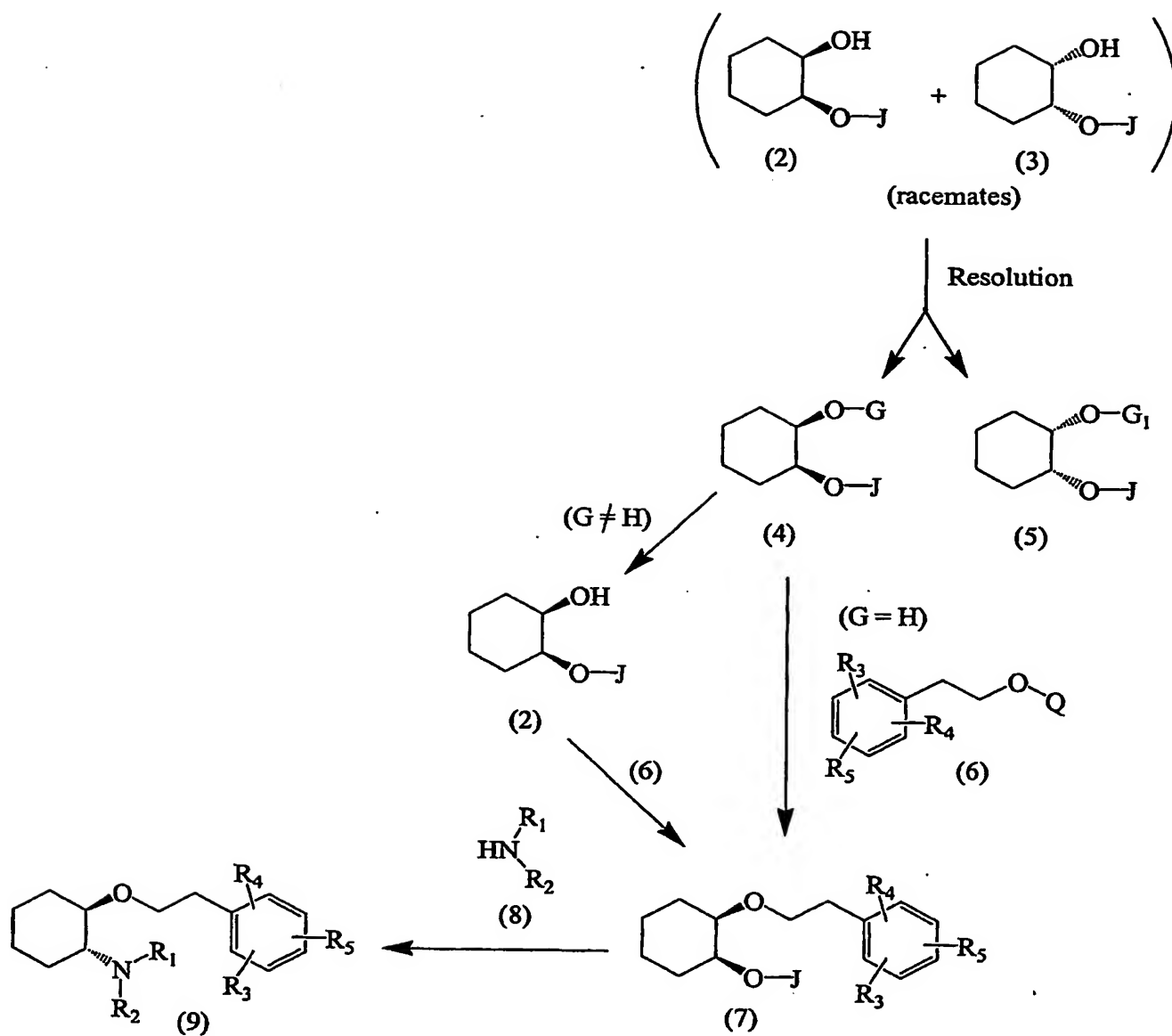
Scheme 3

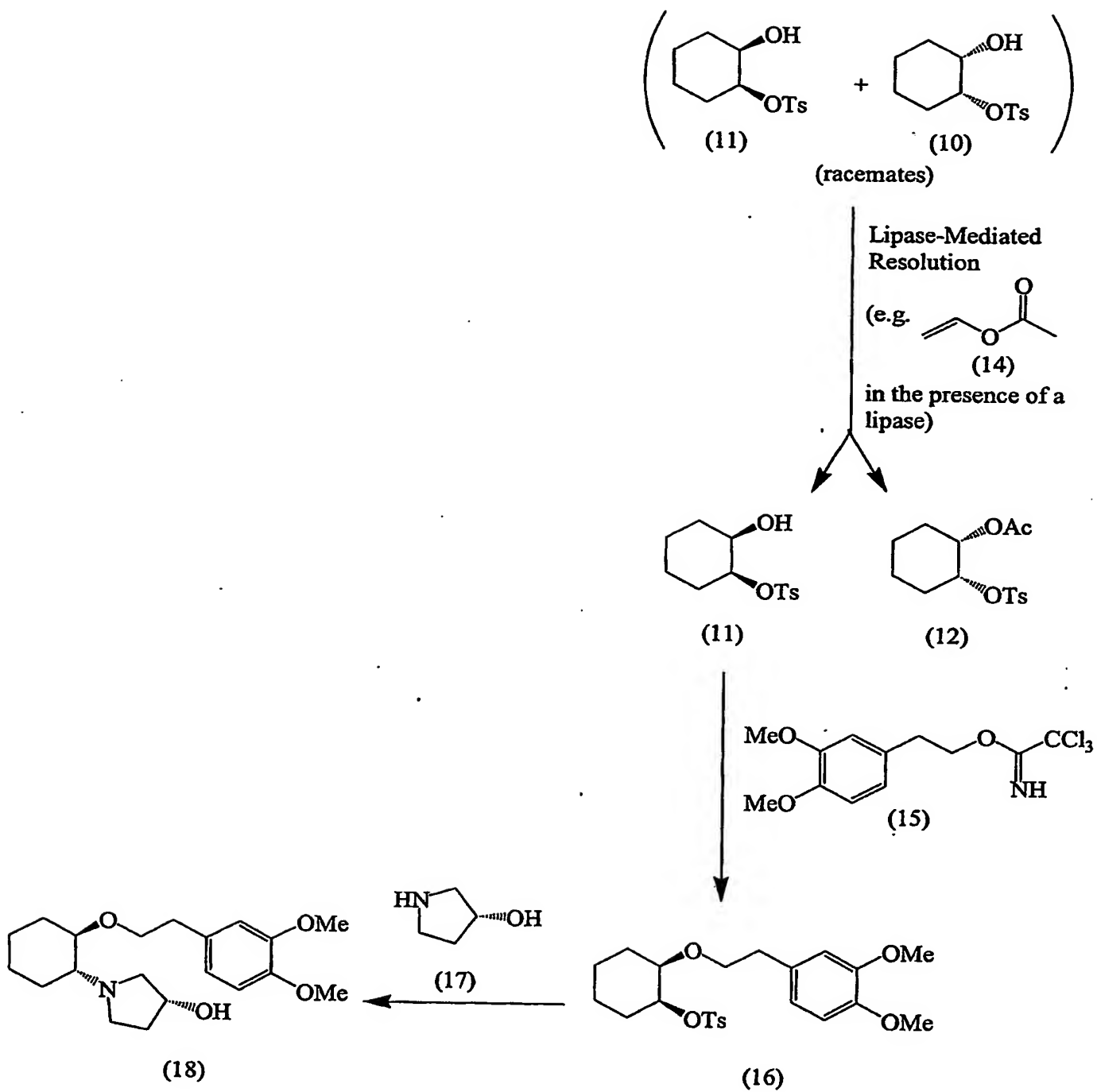


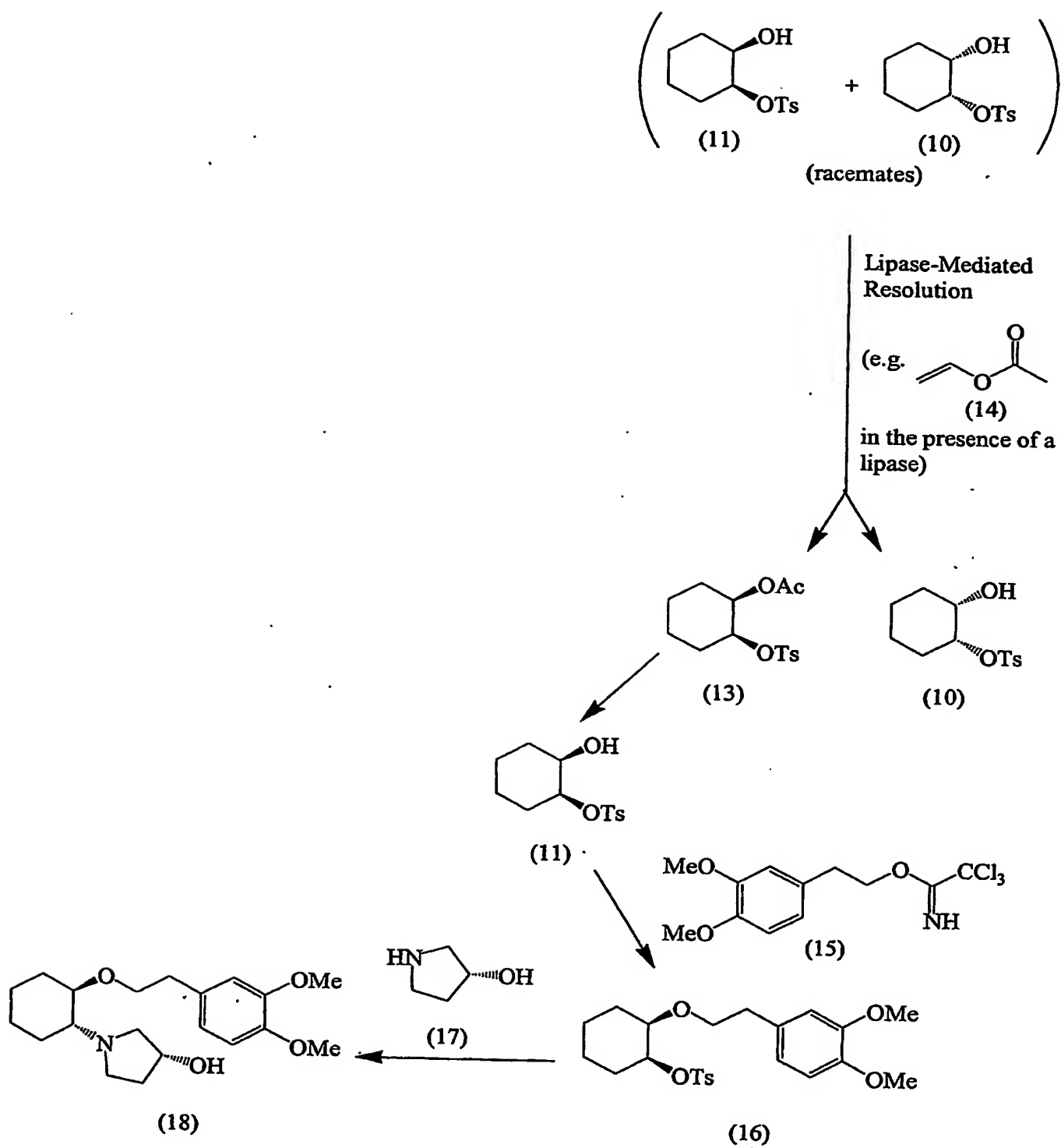
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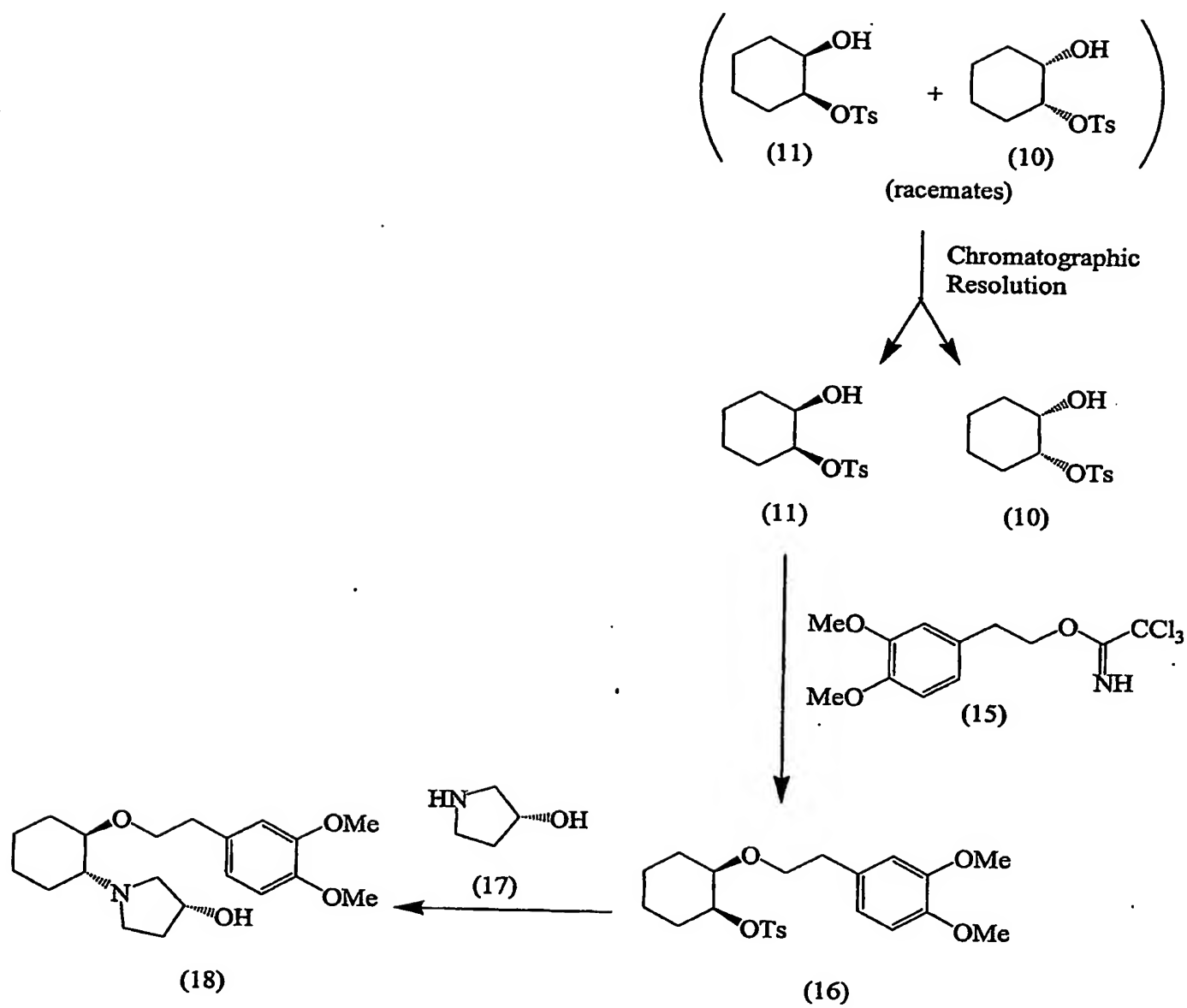


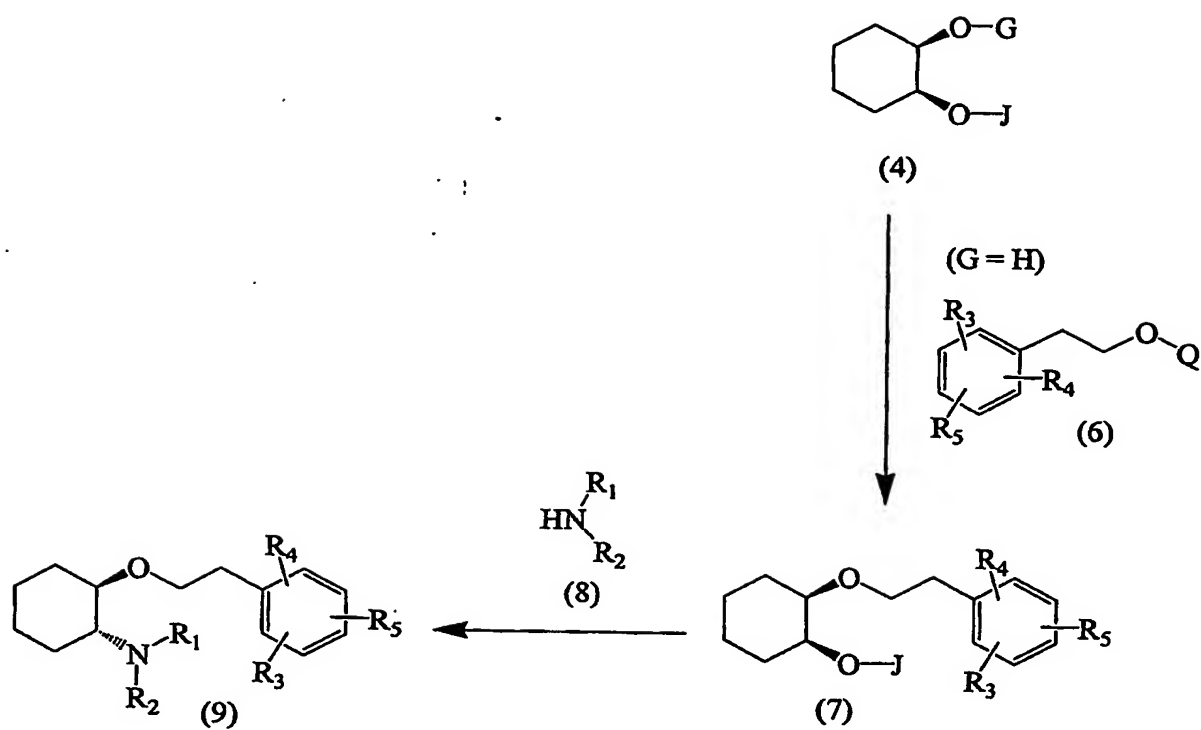
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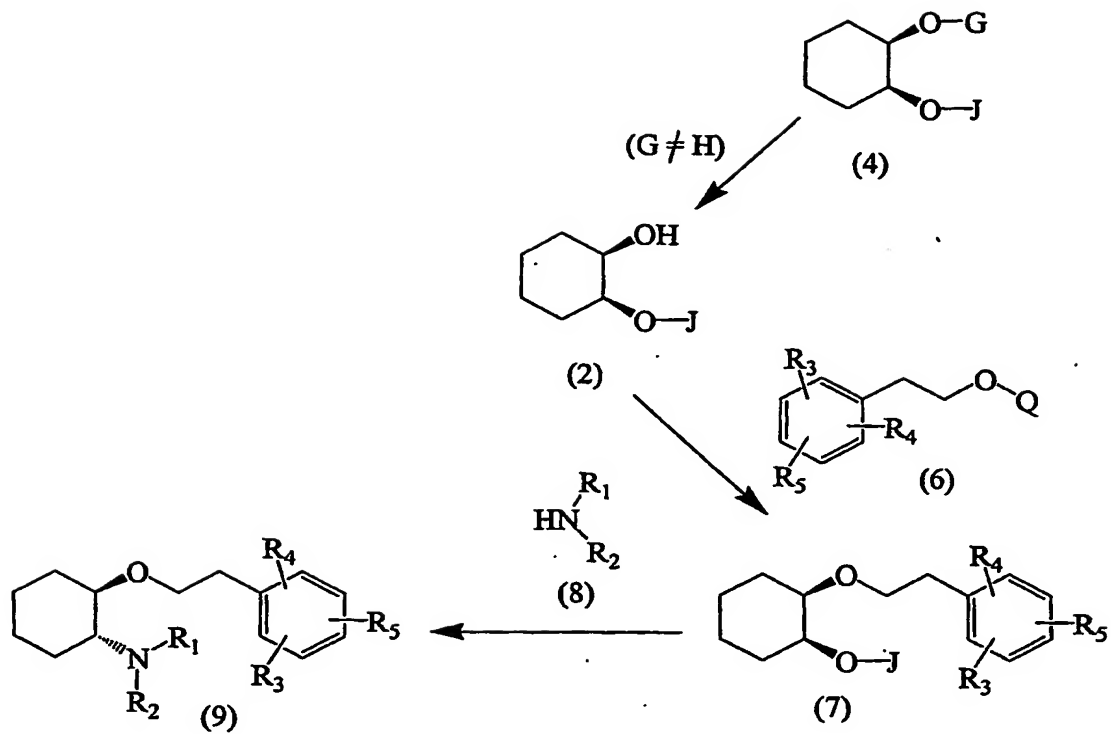


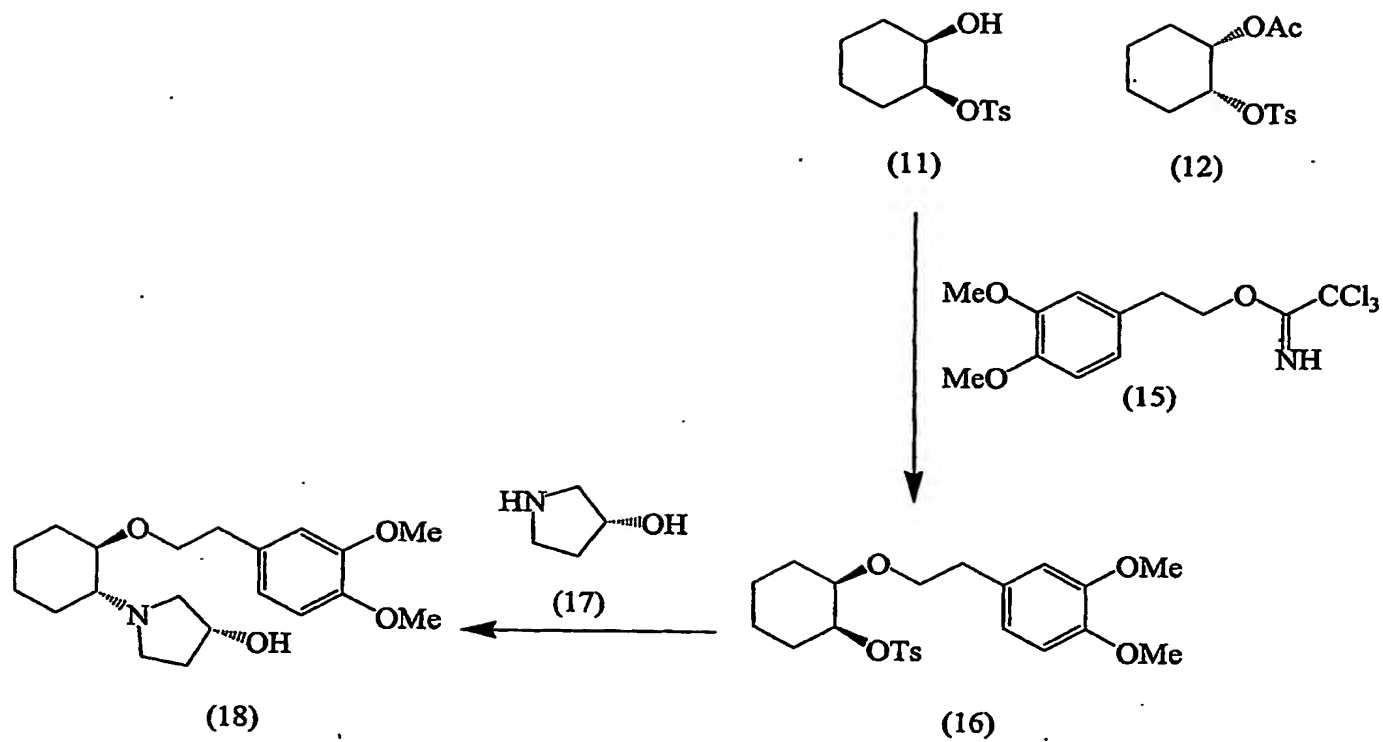
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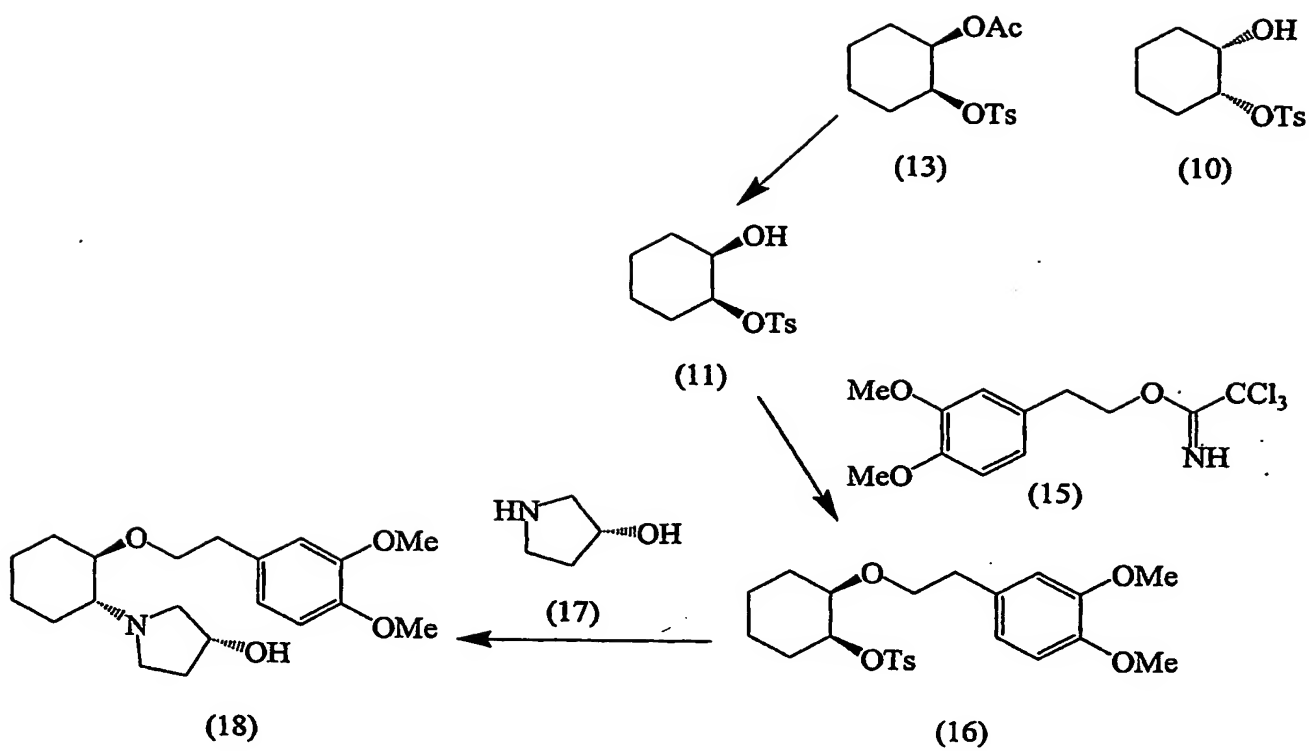
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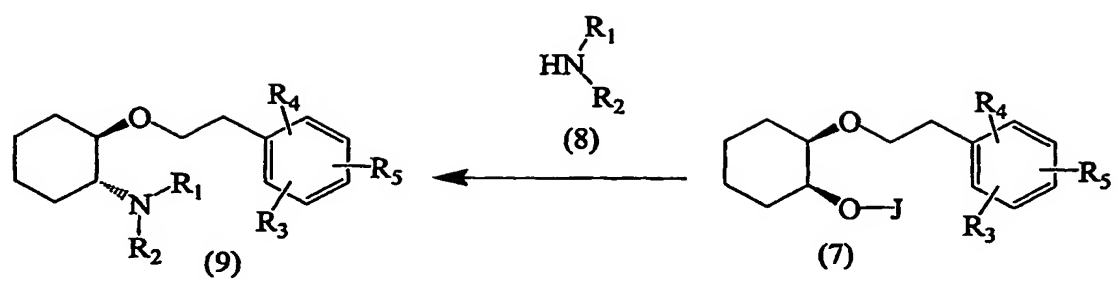
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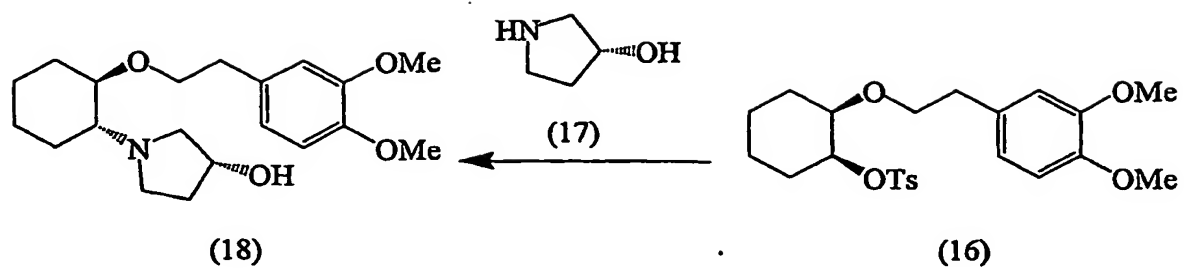
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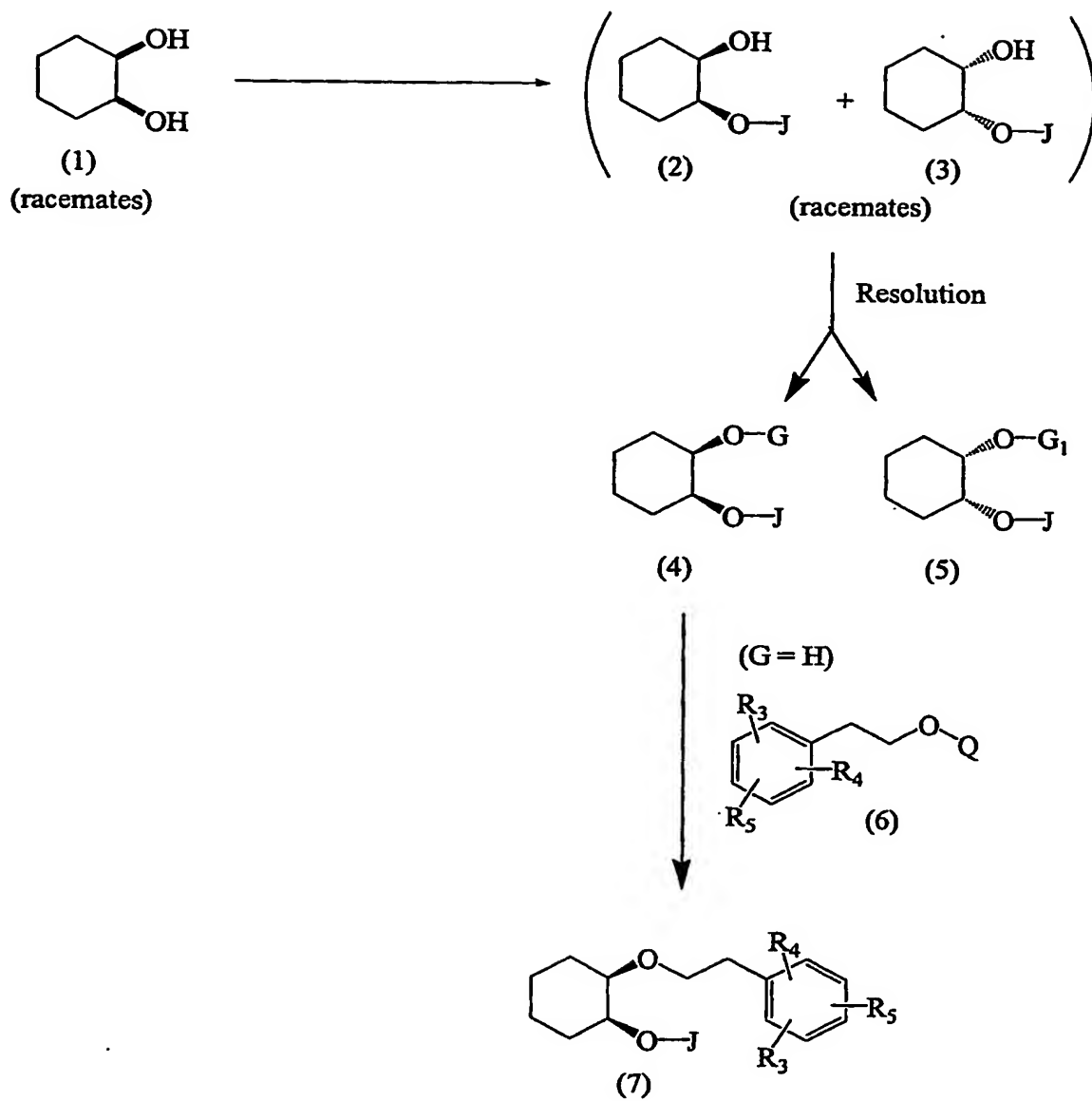
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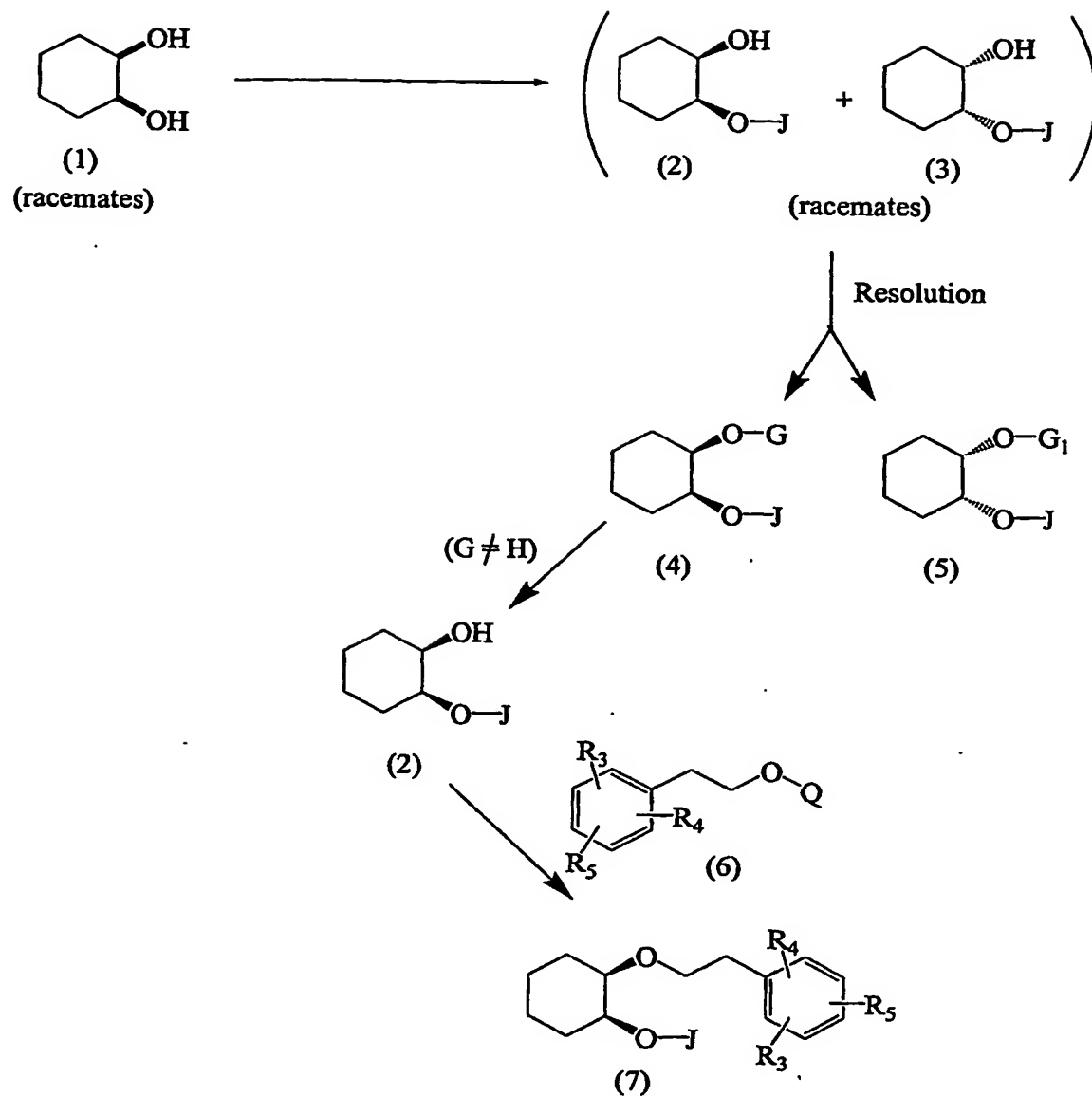
Scheme 11

Scheme 12

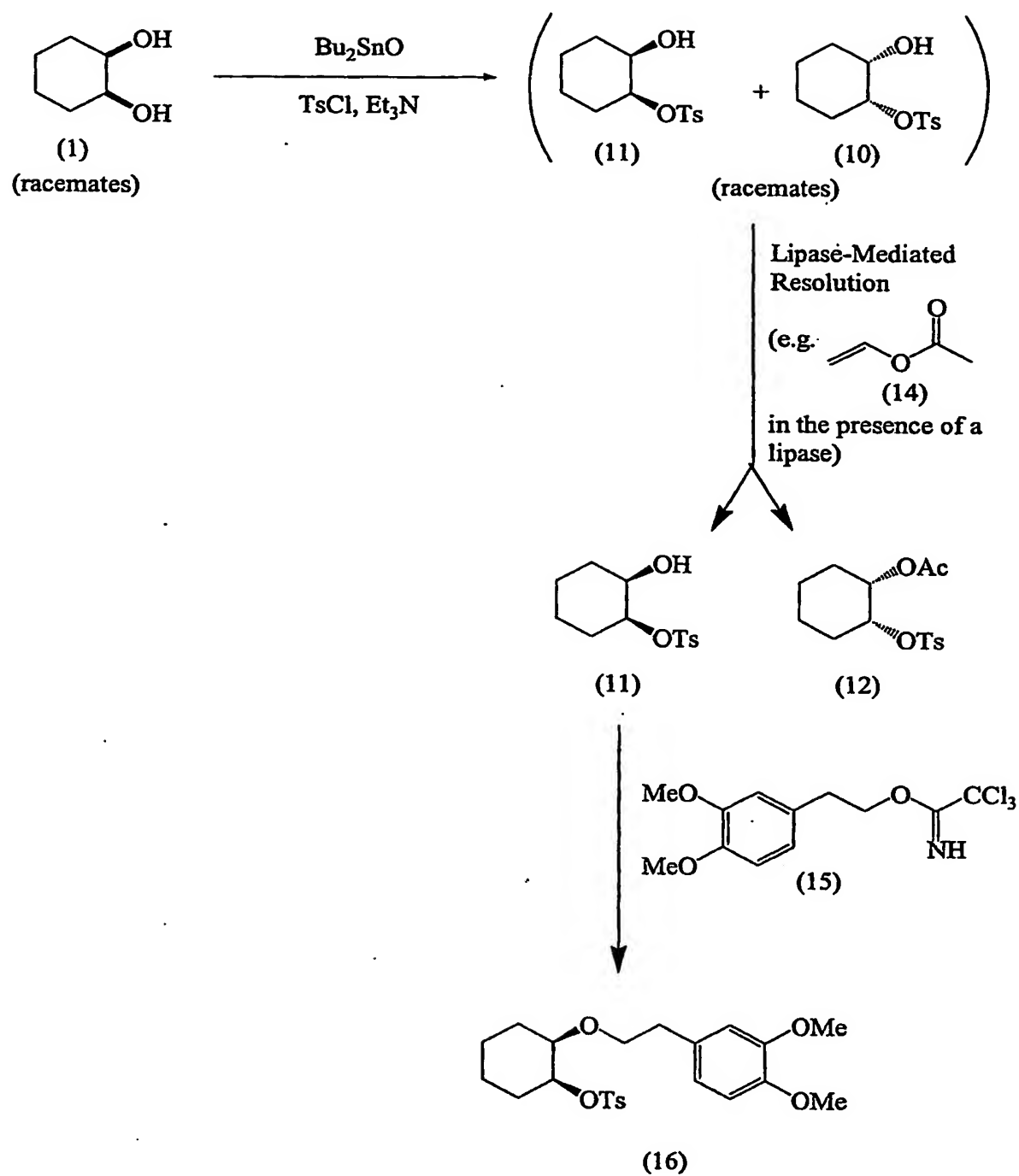
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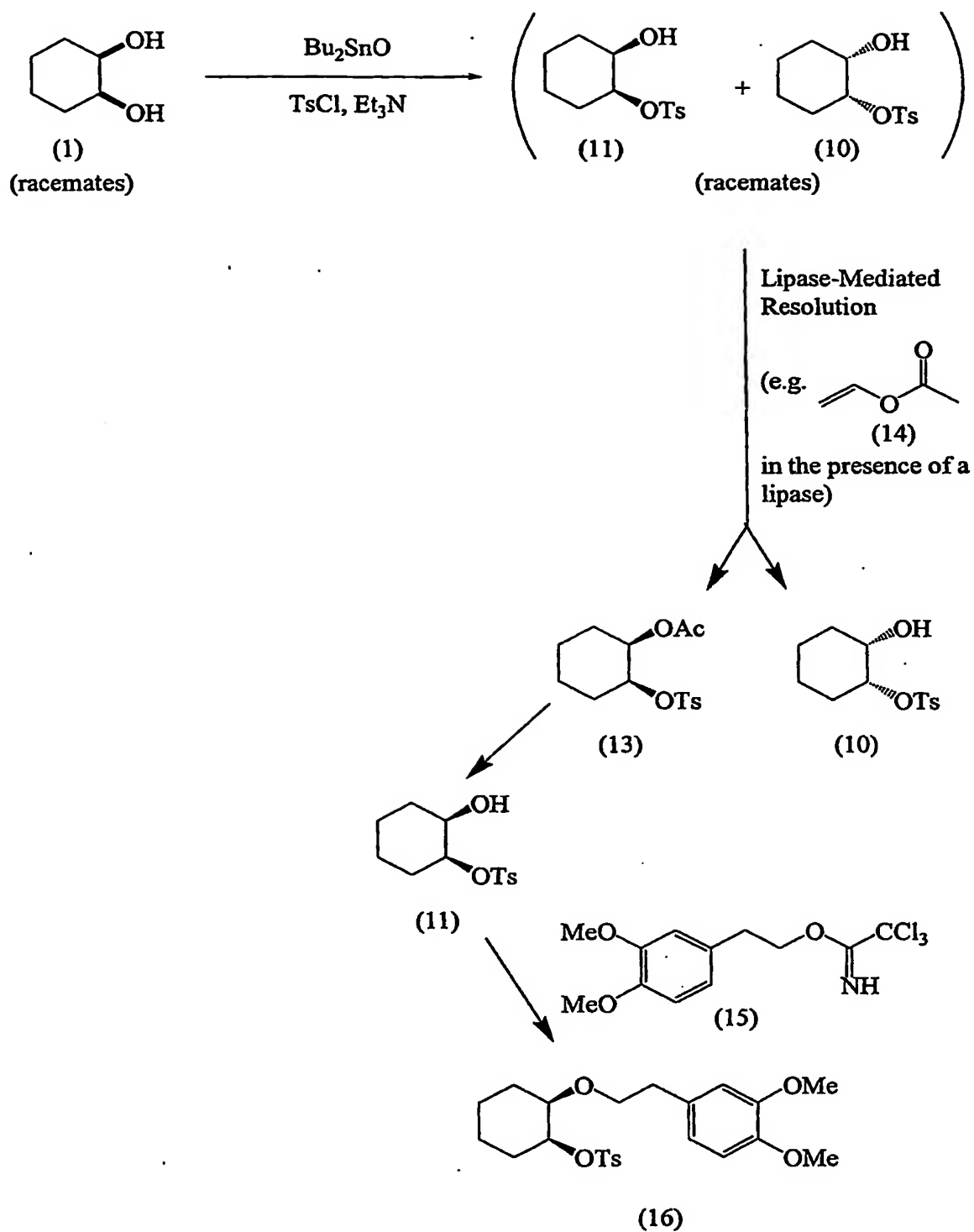
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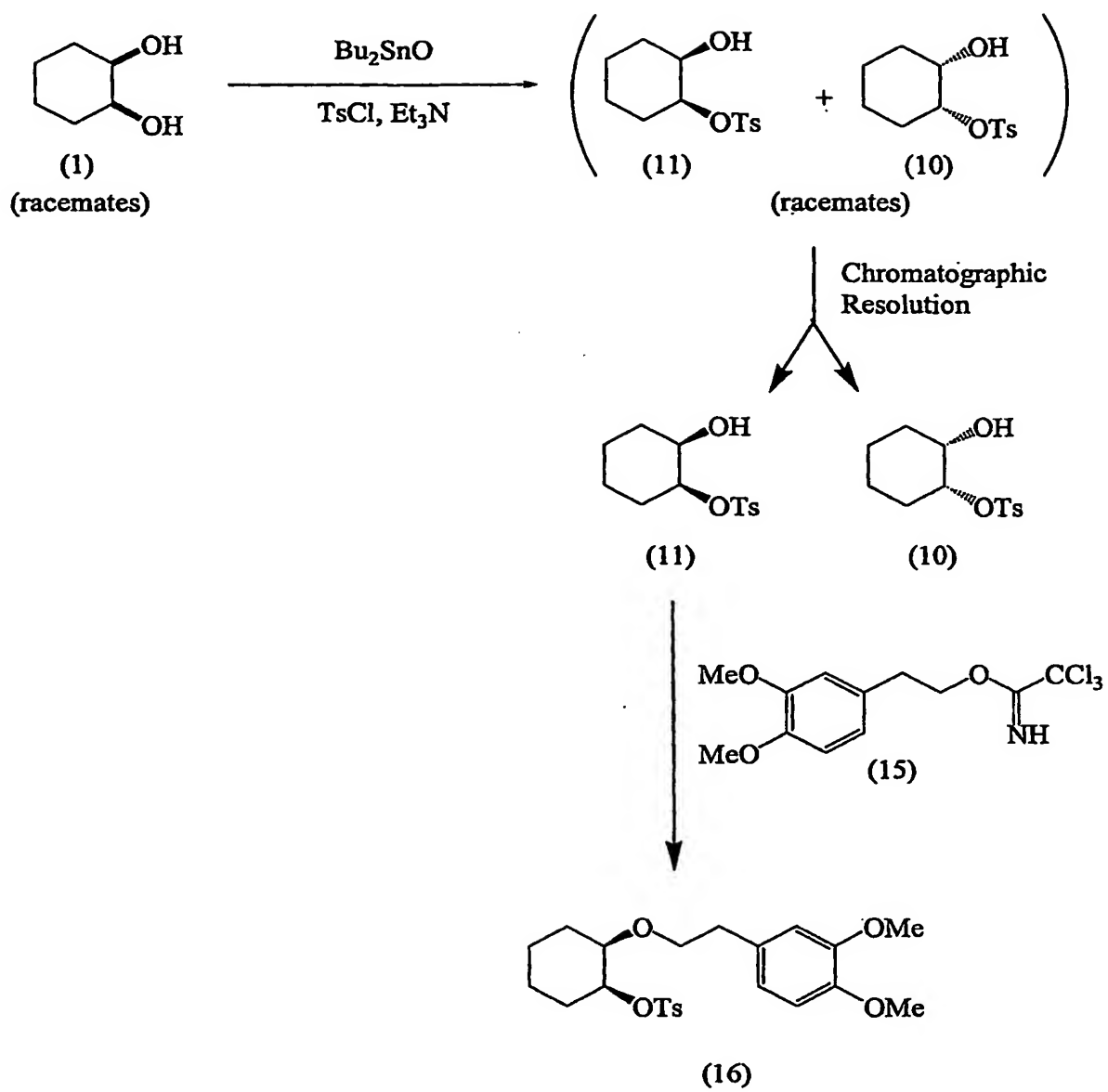
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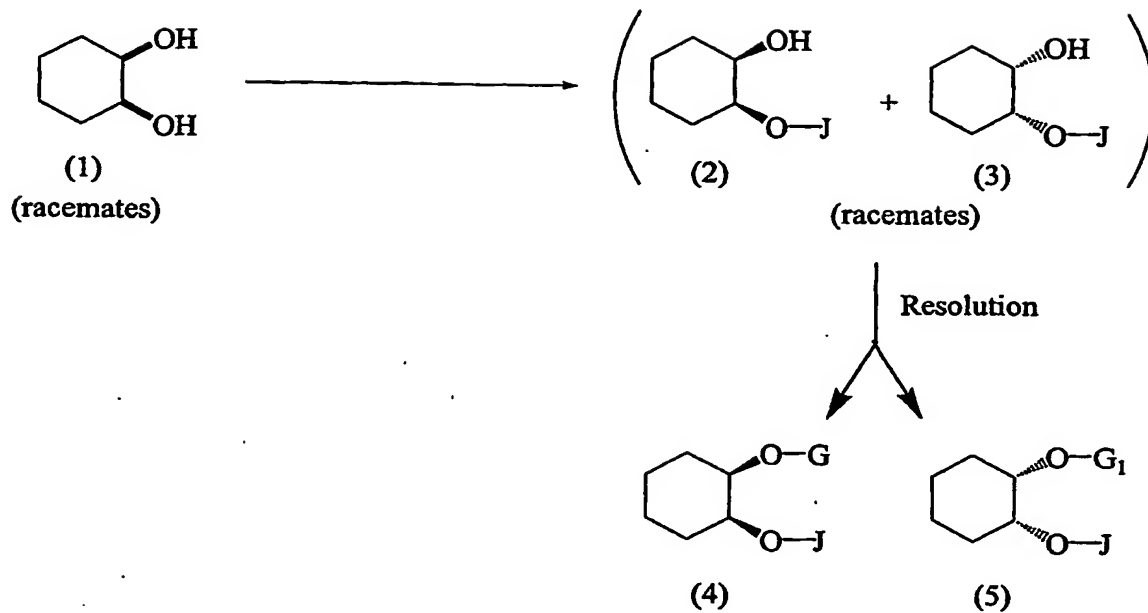
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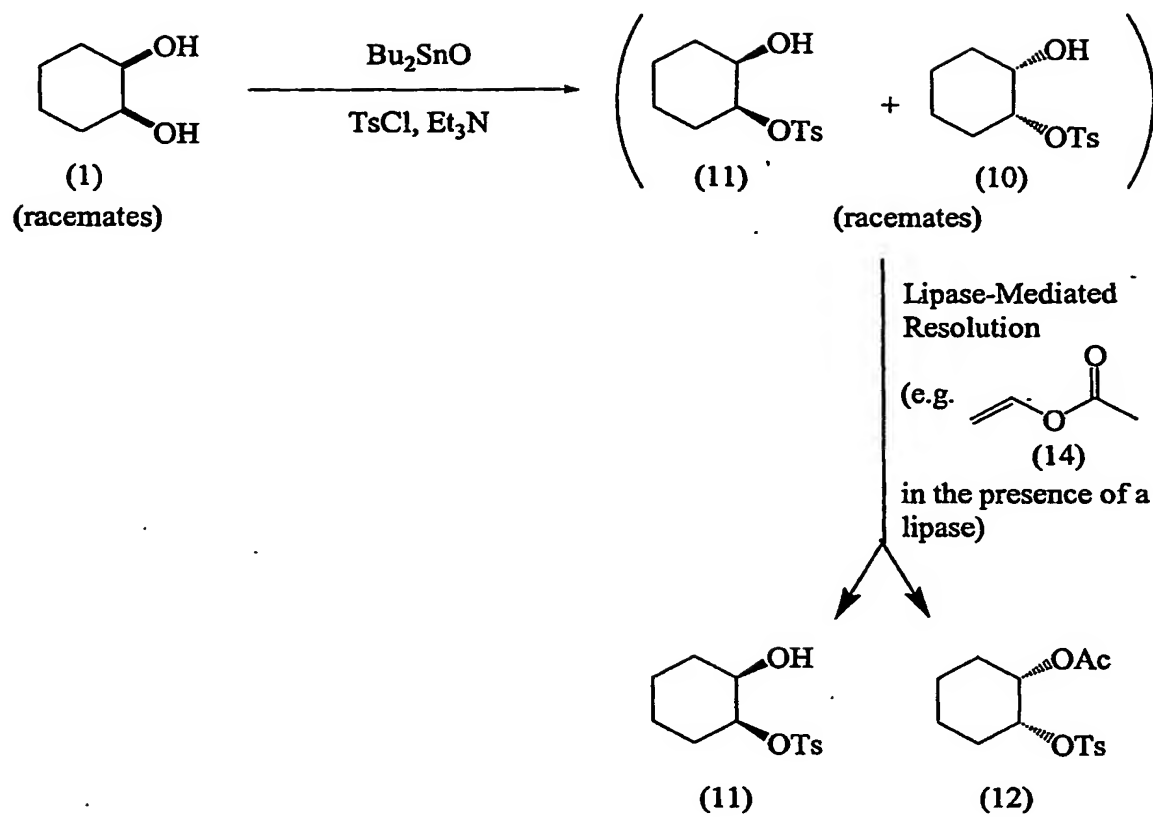
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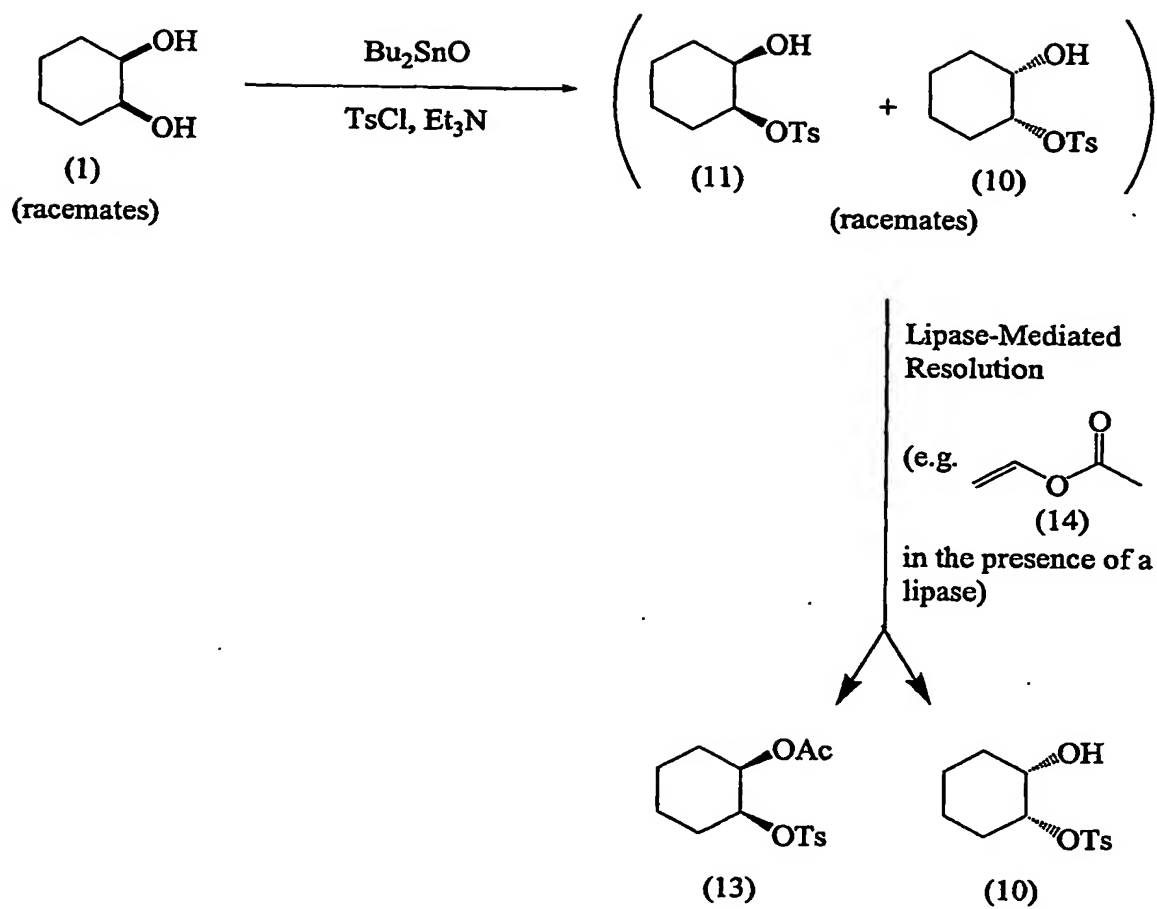


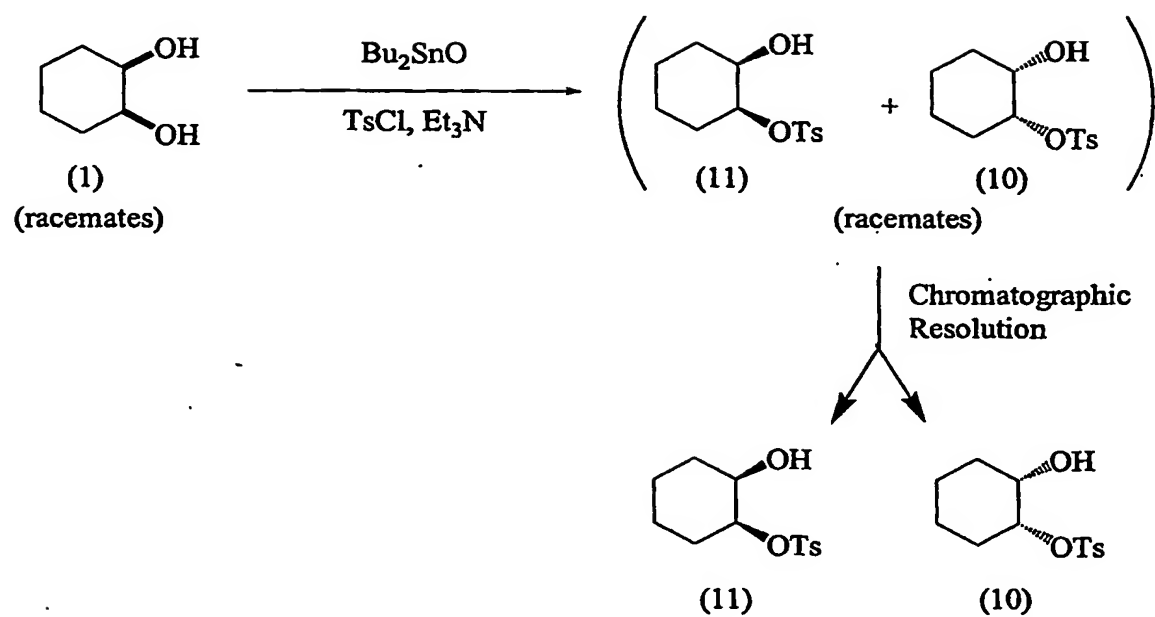
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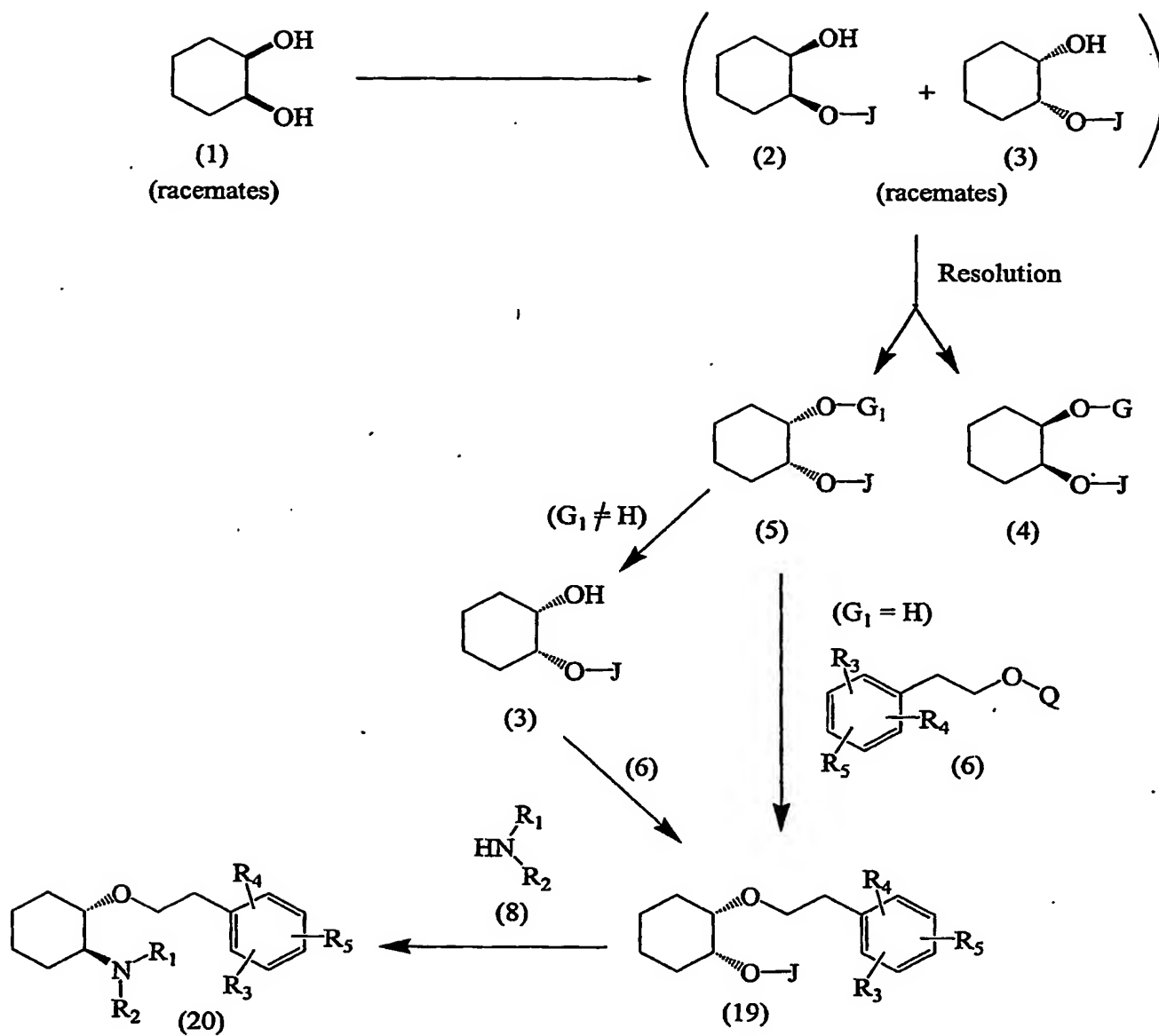
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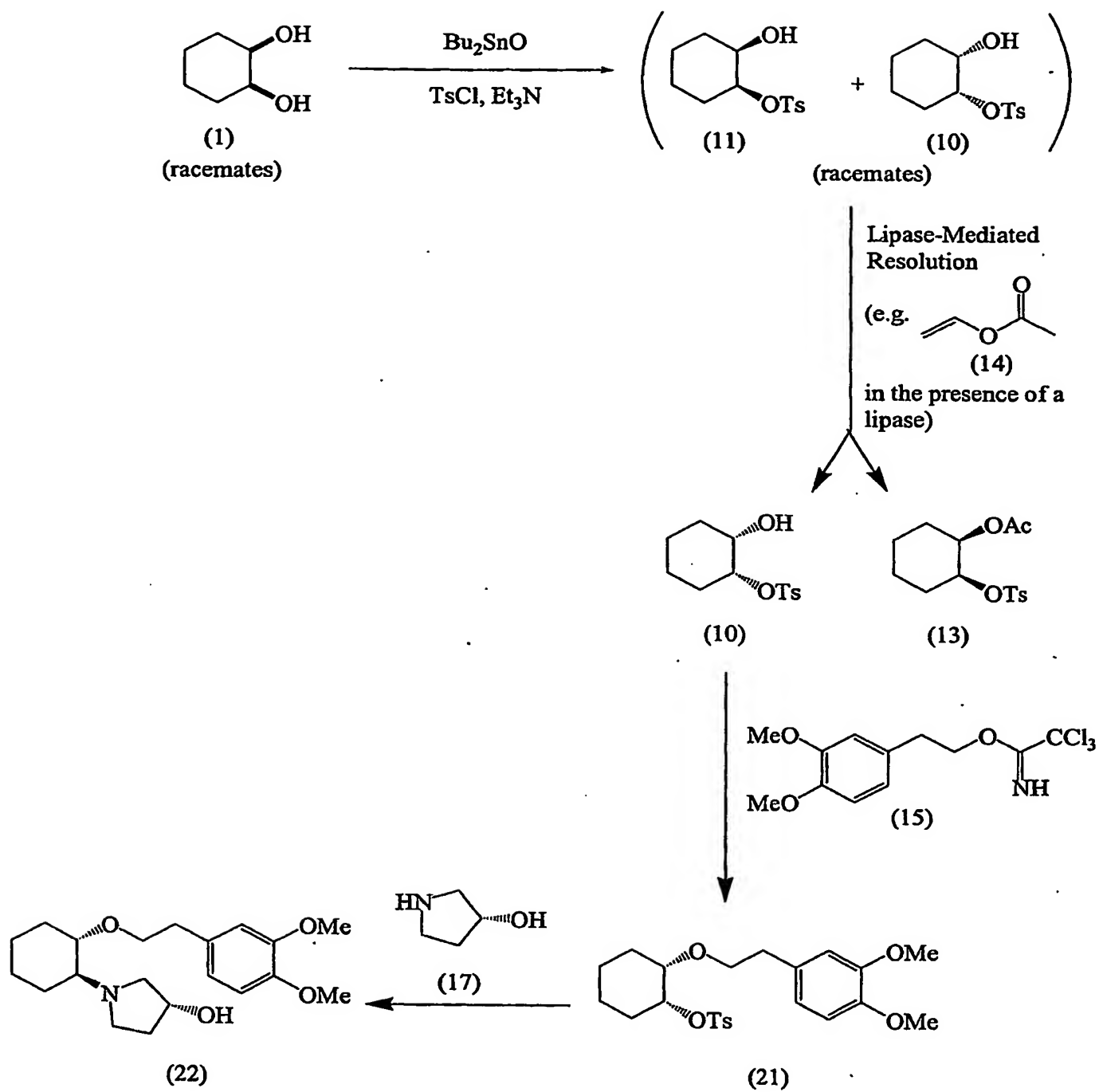
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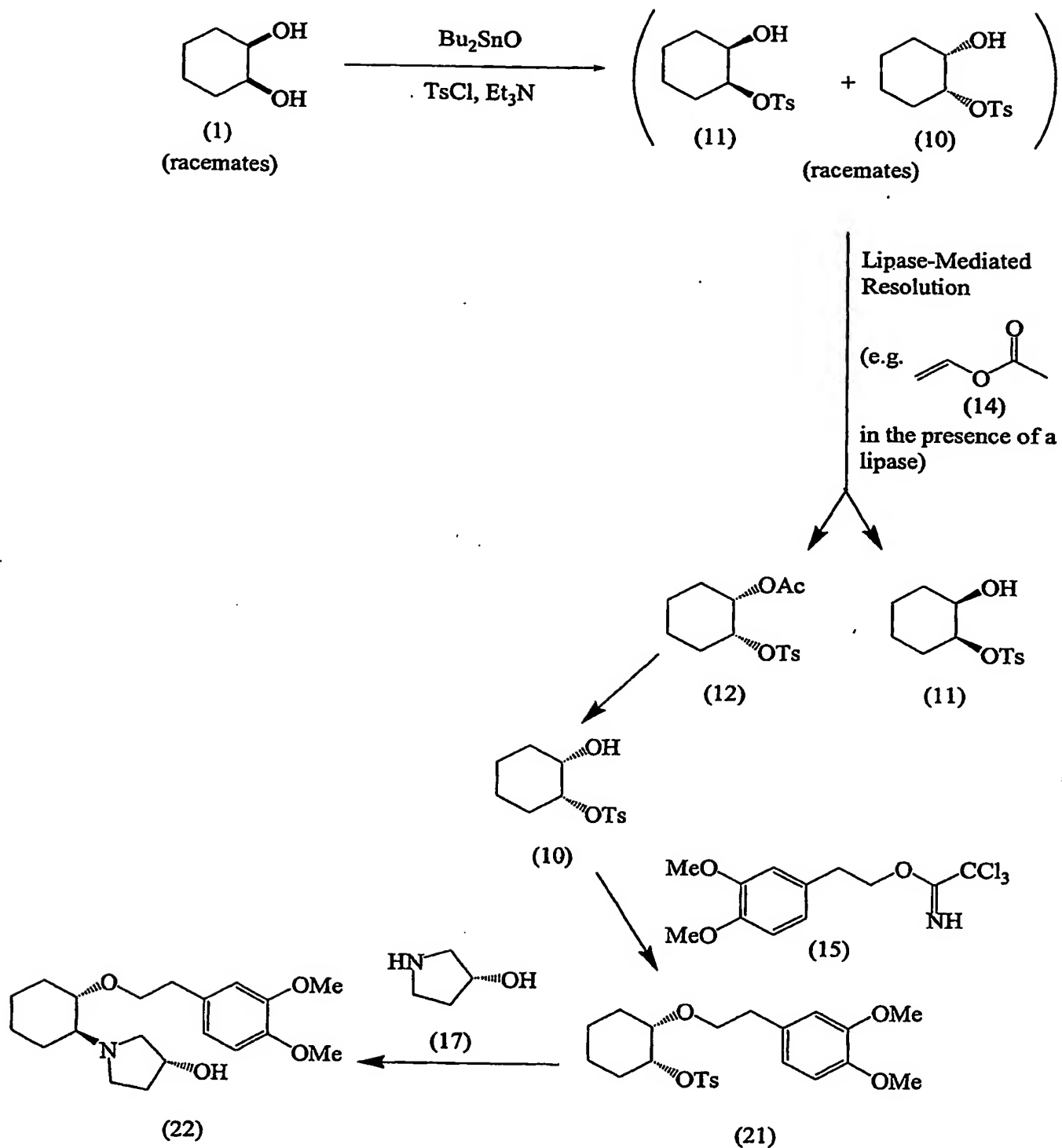
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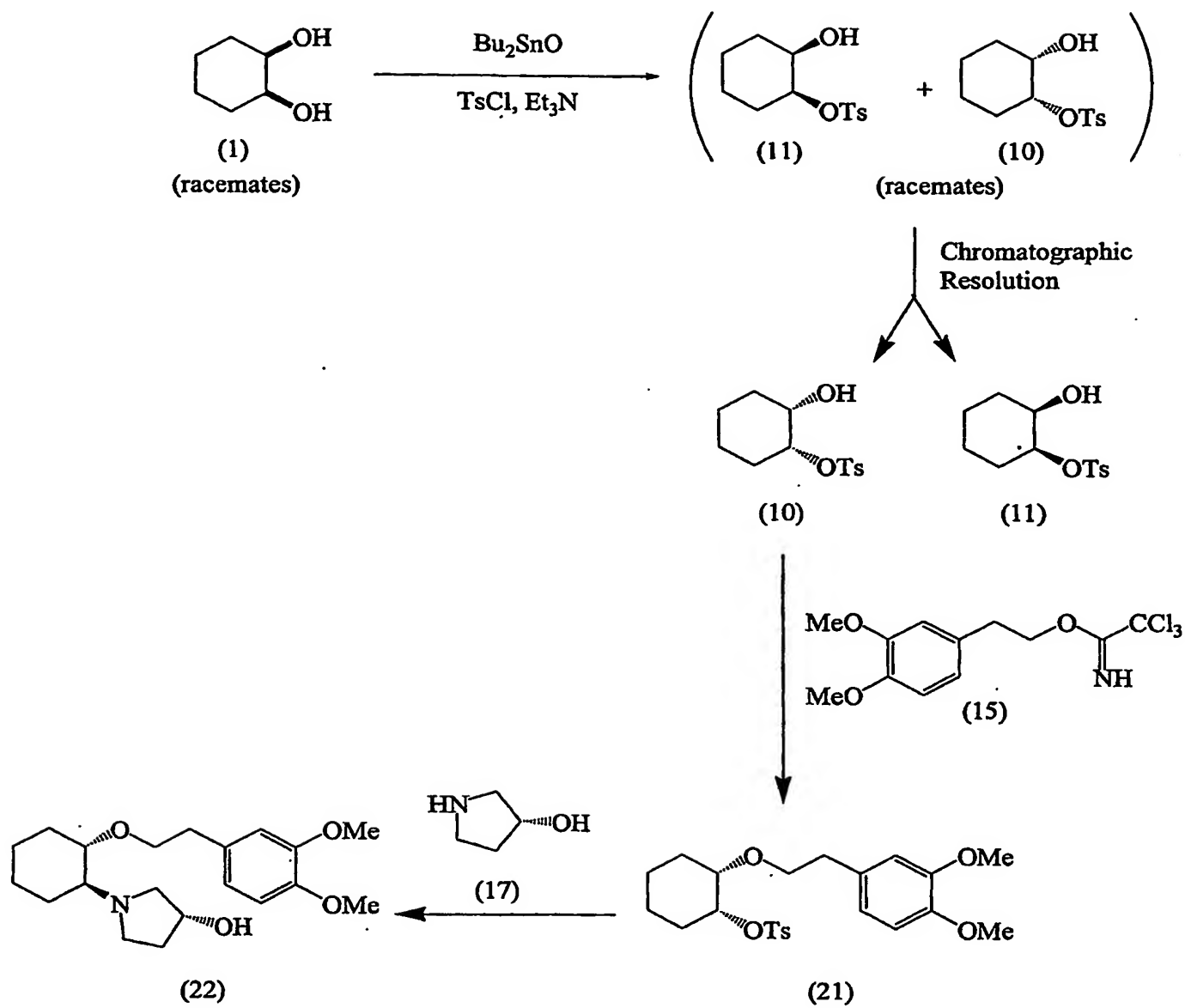
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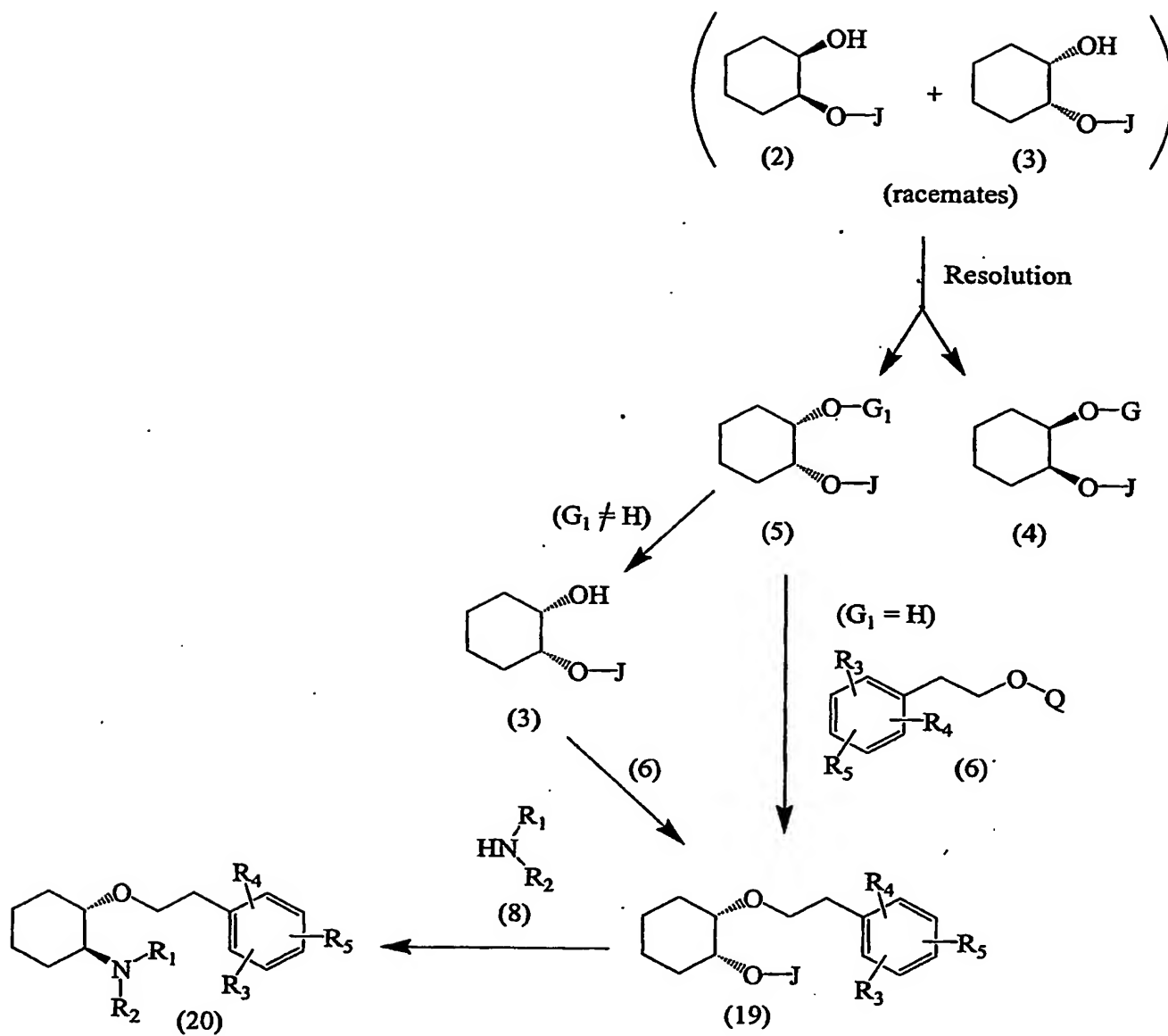
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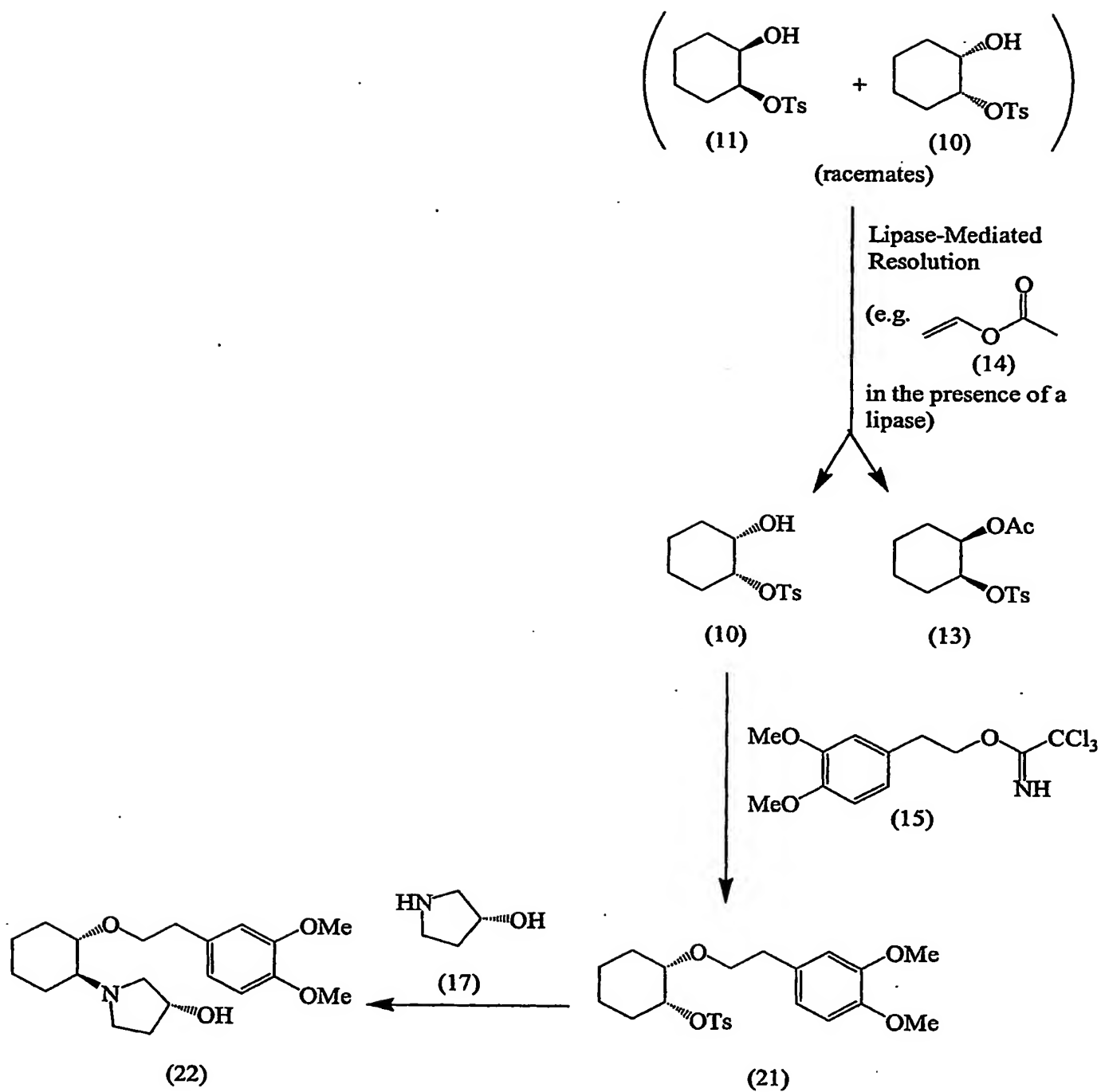
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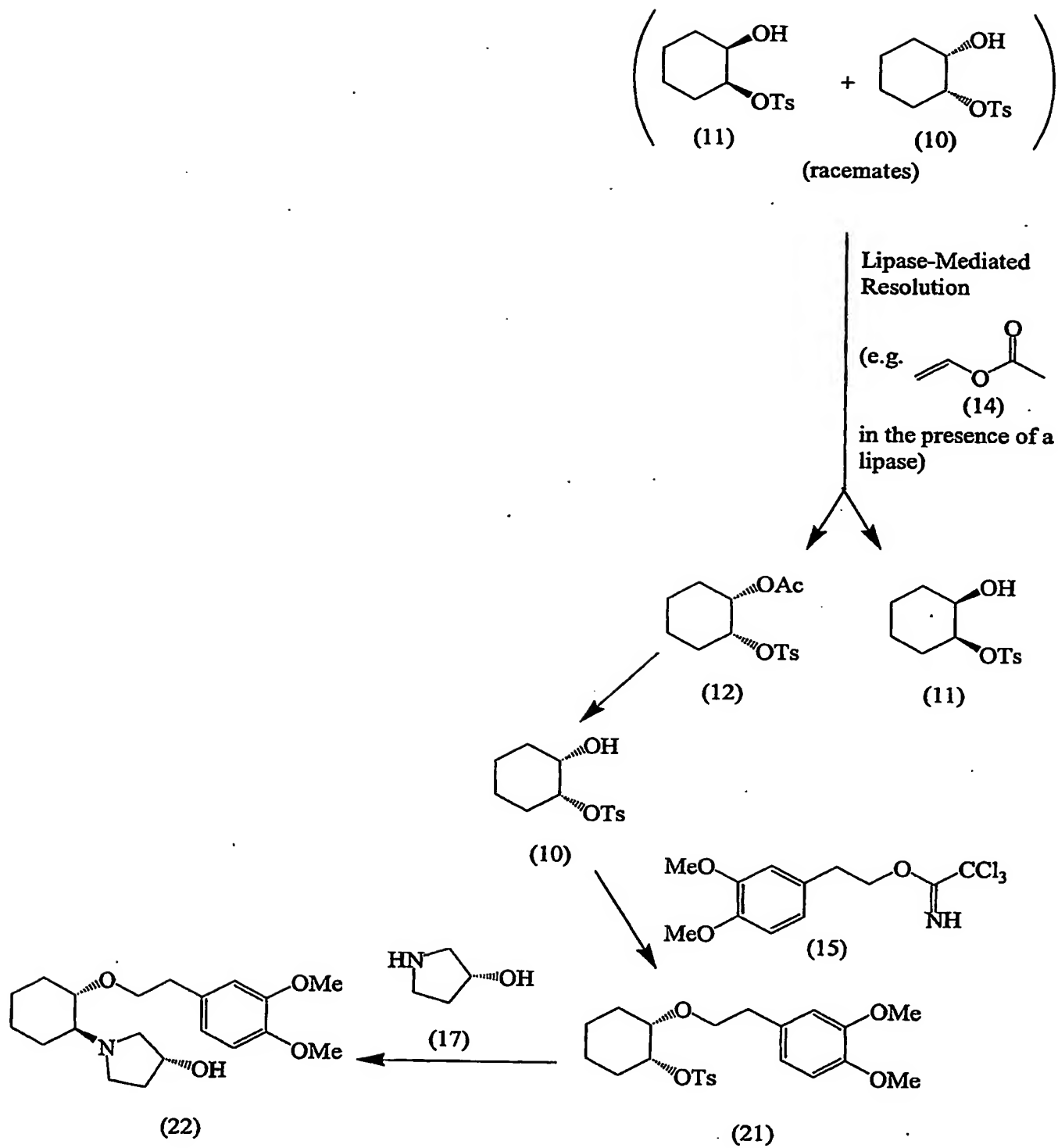
Scheme 25

Scheme 26

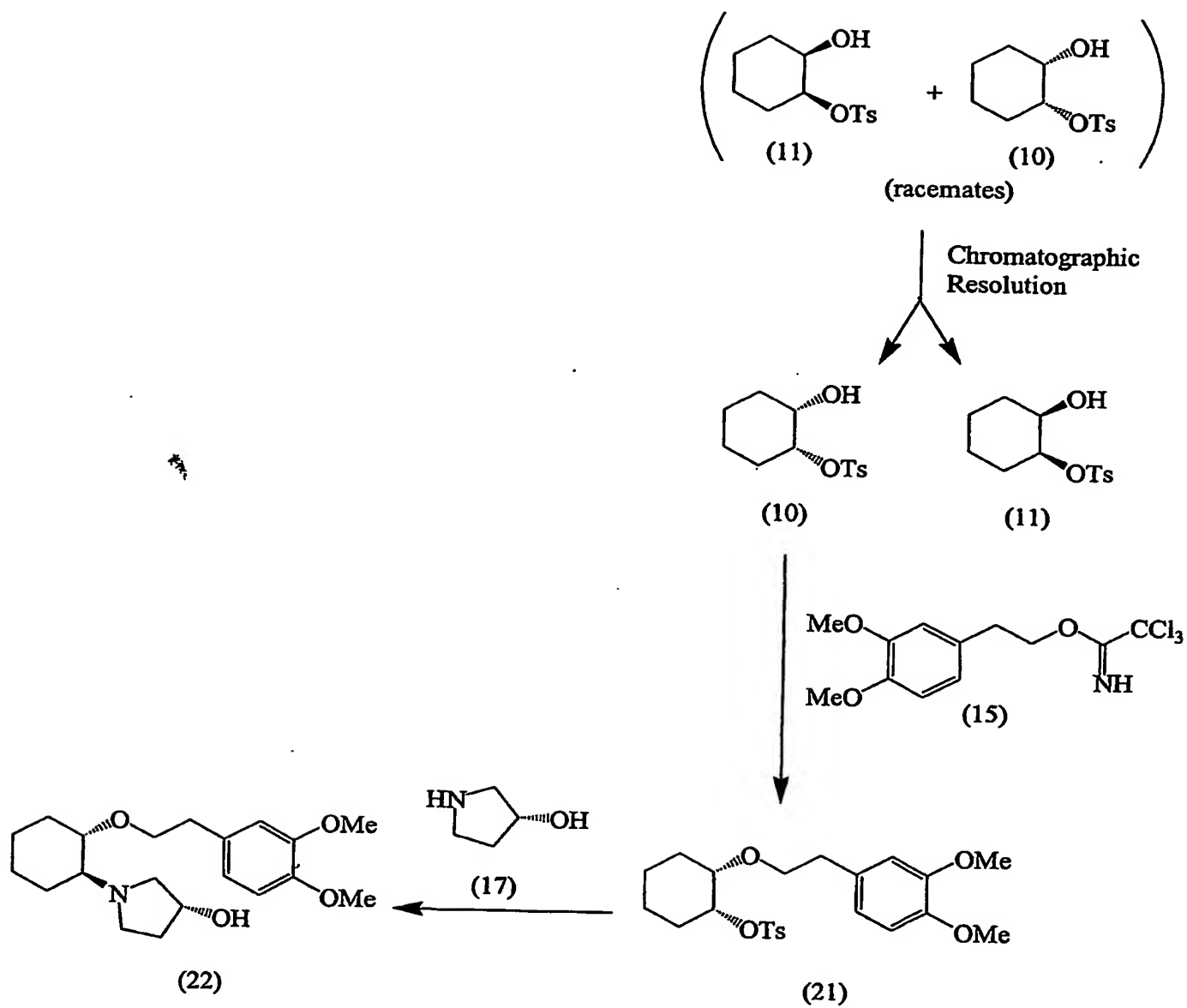
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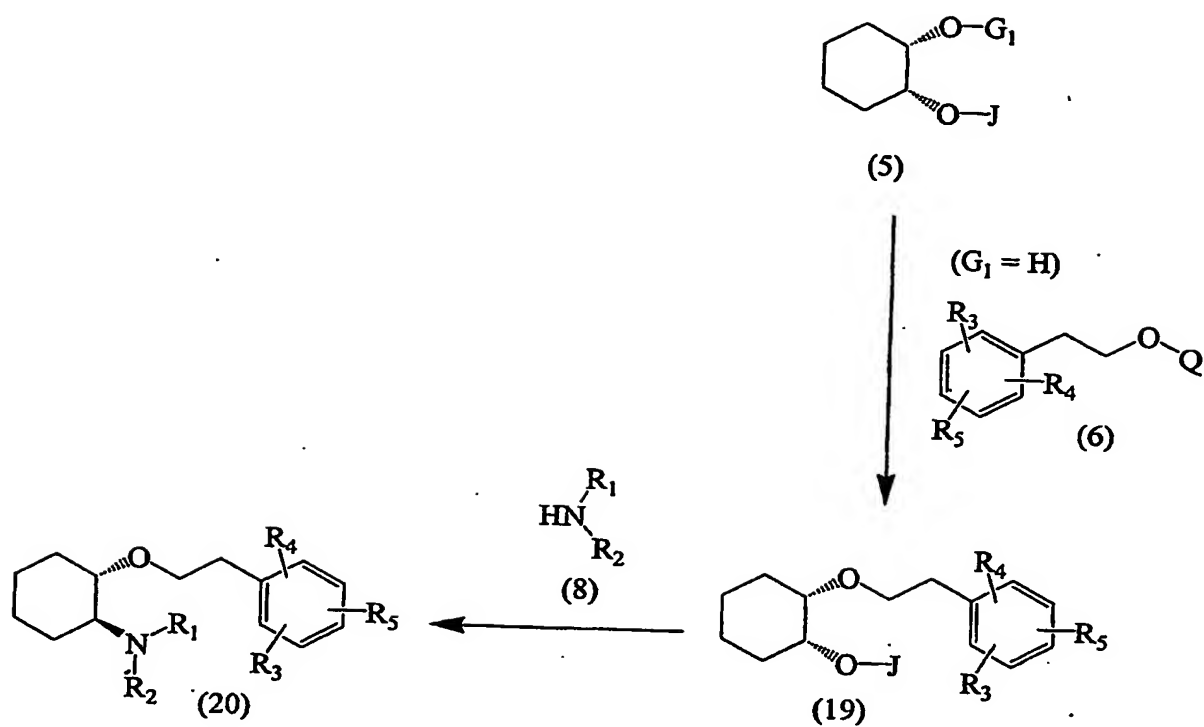
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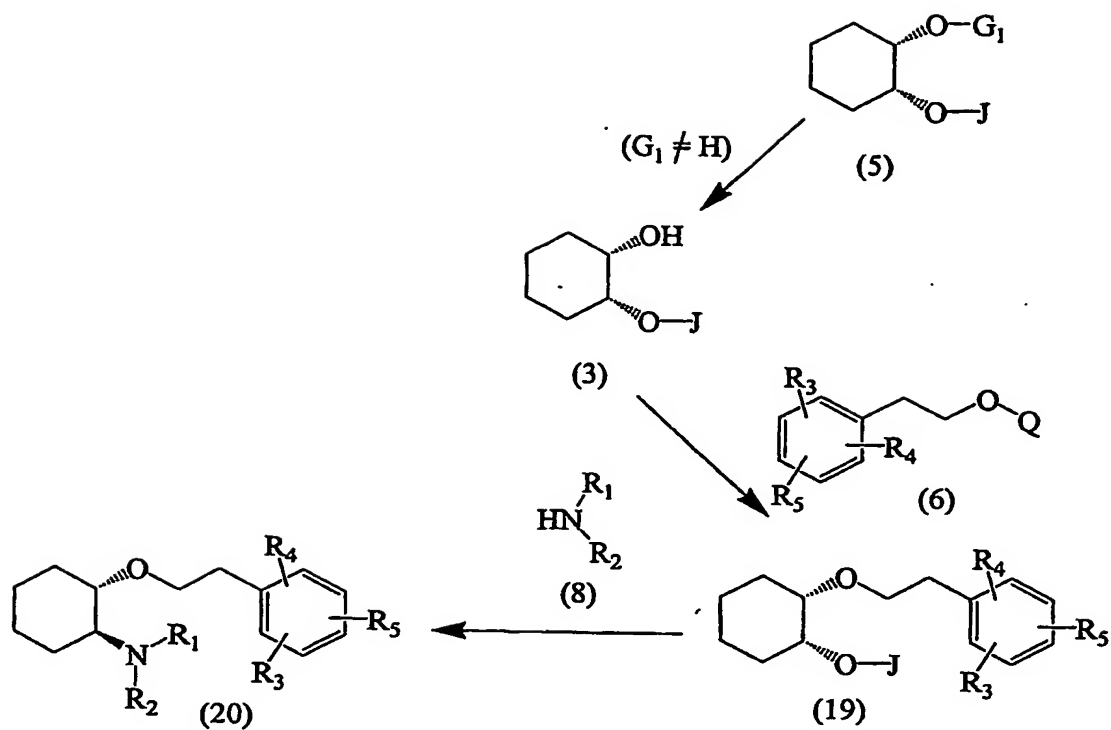
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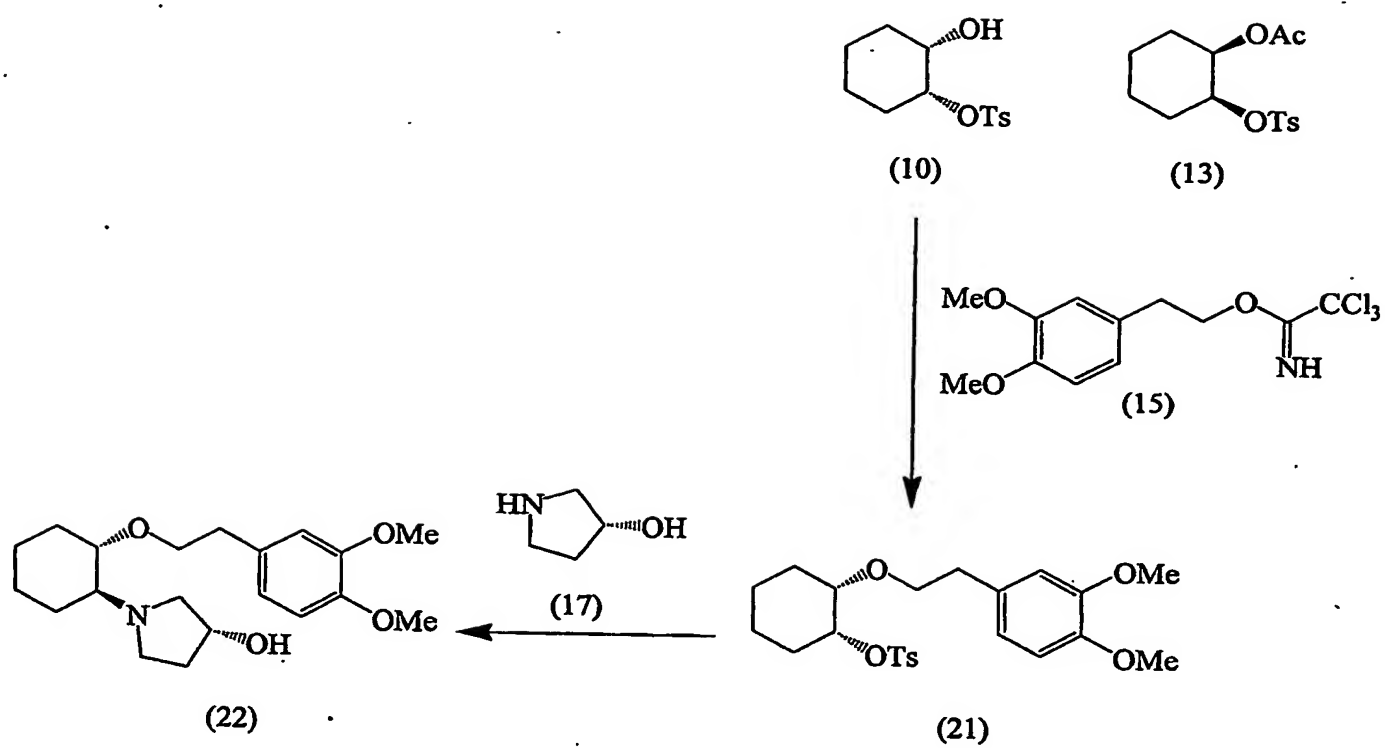
Scheme 30

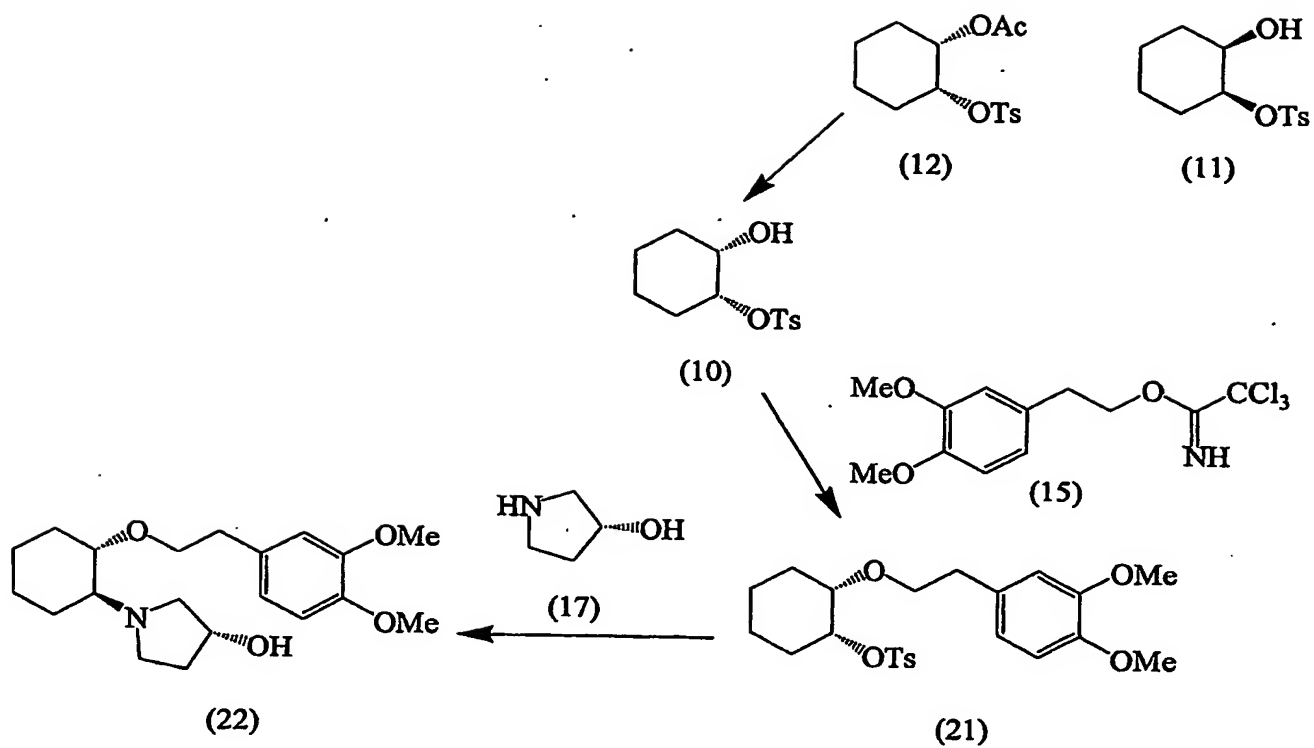
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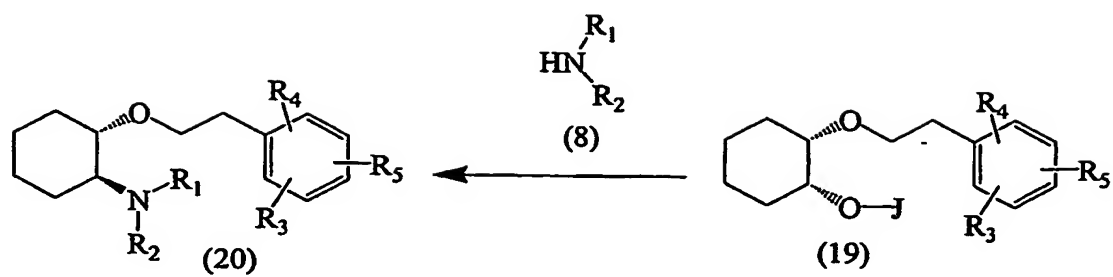


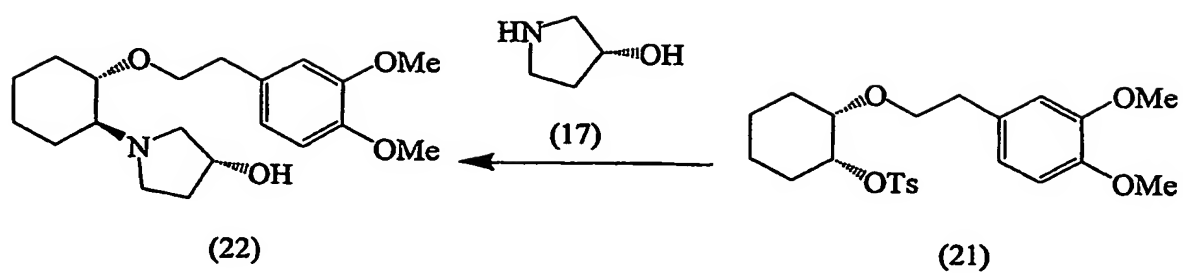
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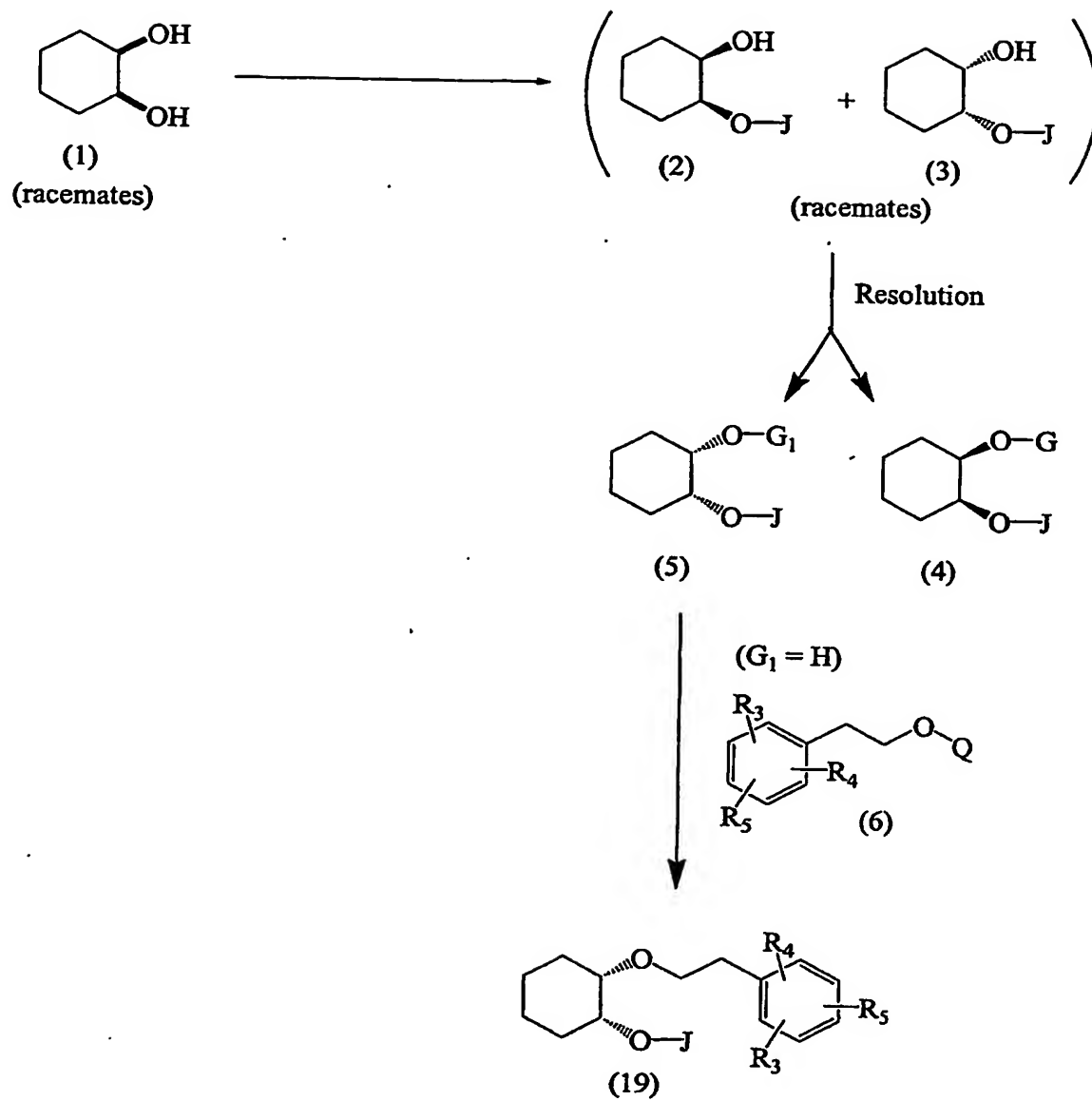
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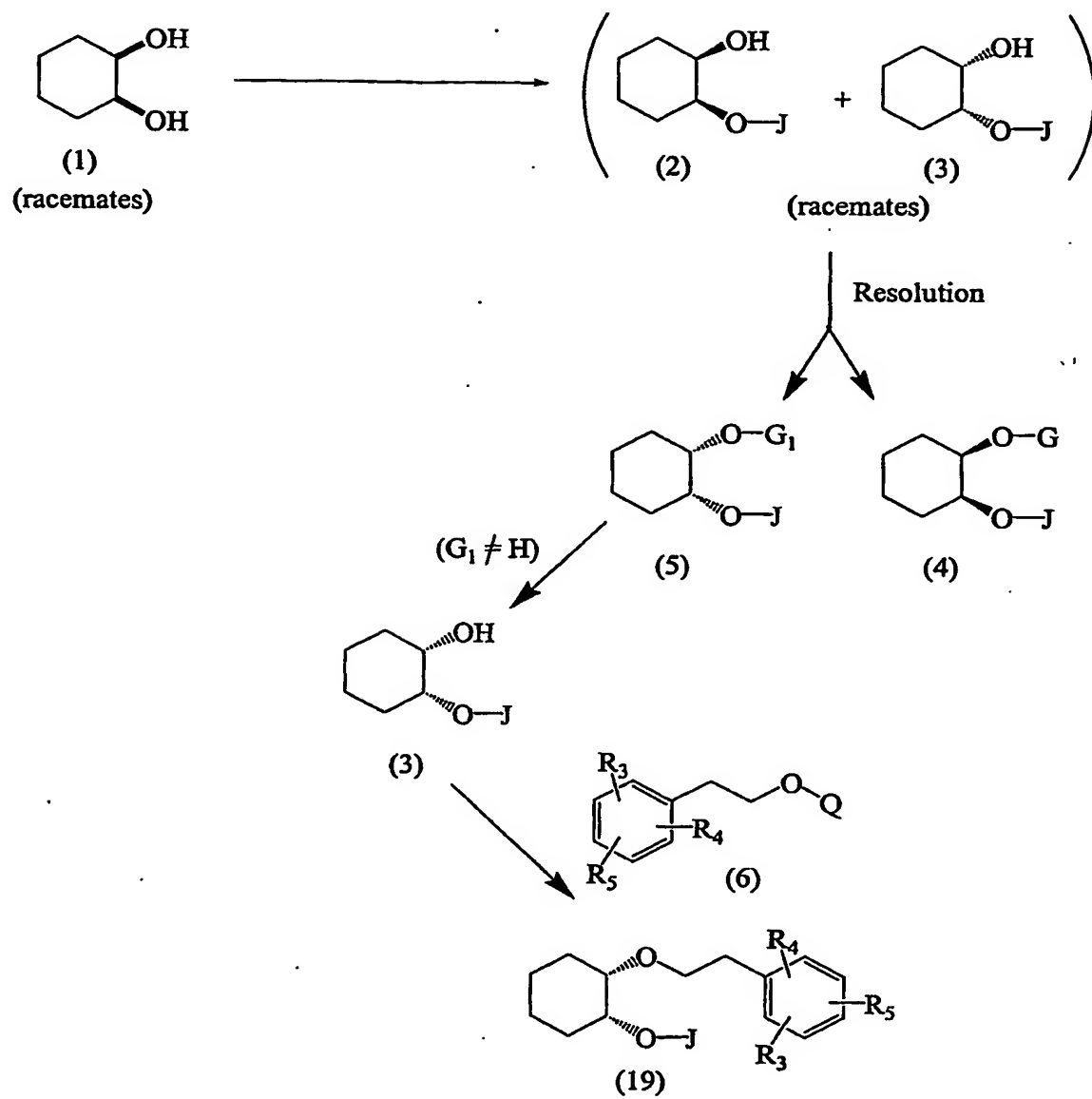
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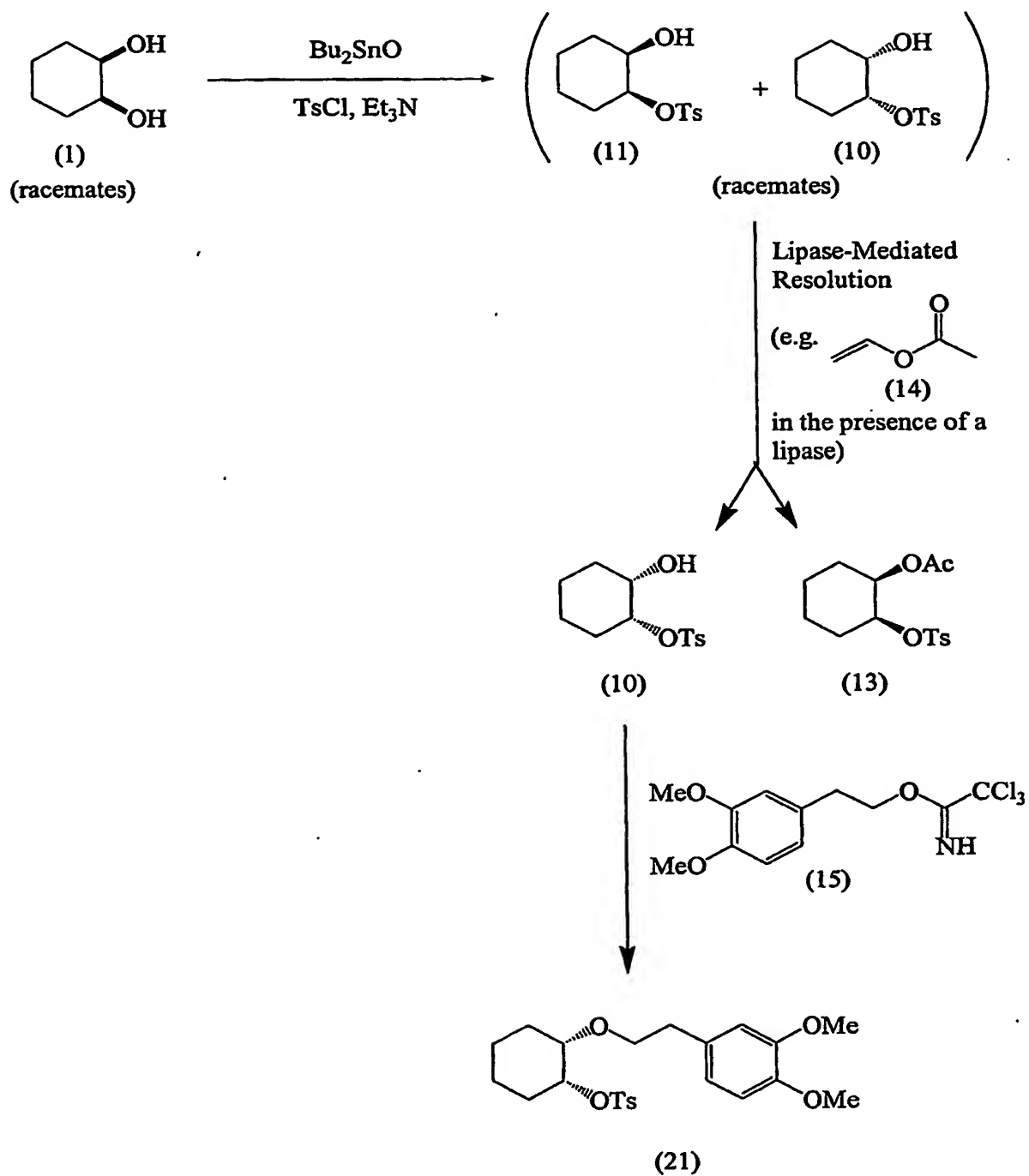
Scheme 35

Scheme 36

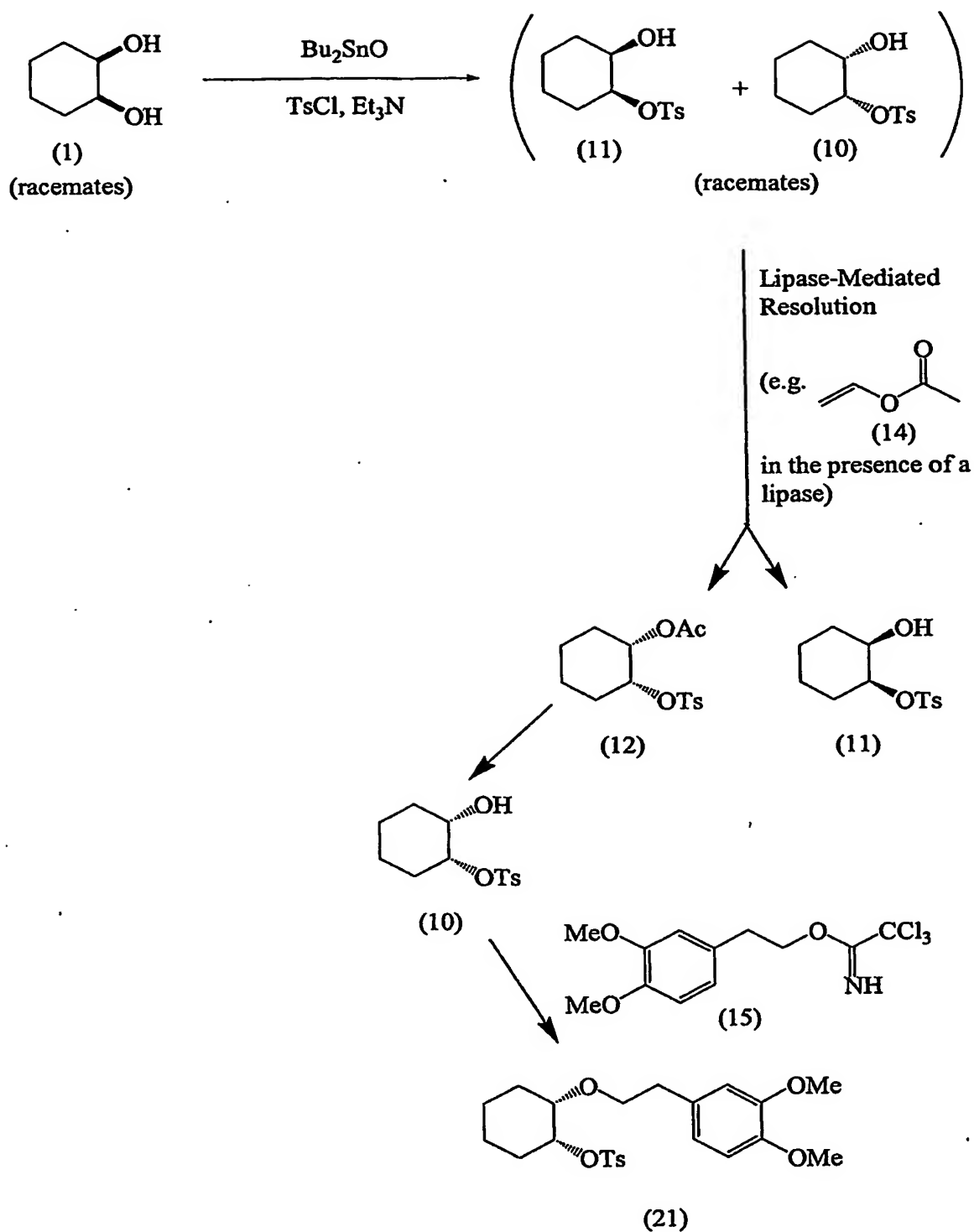
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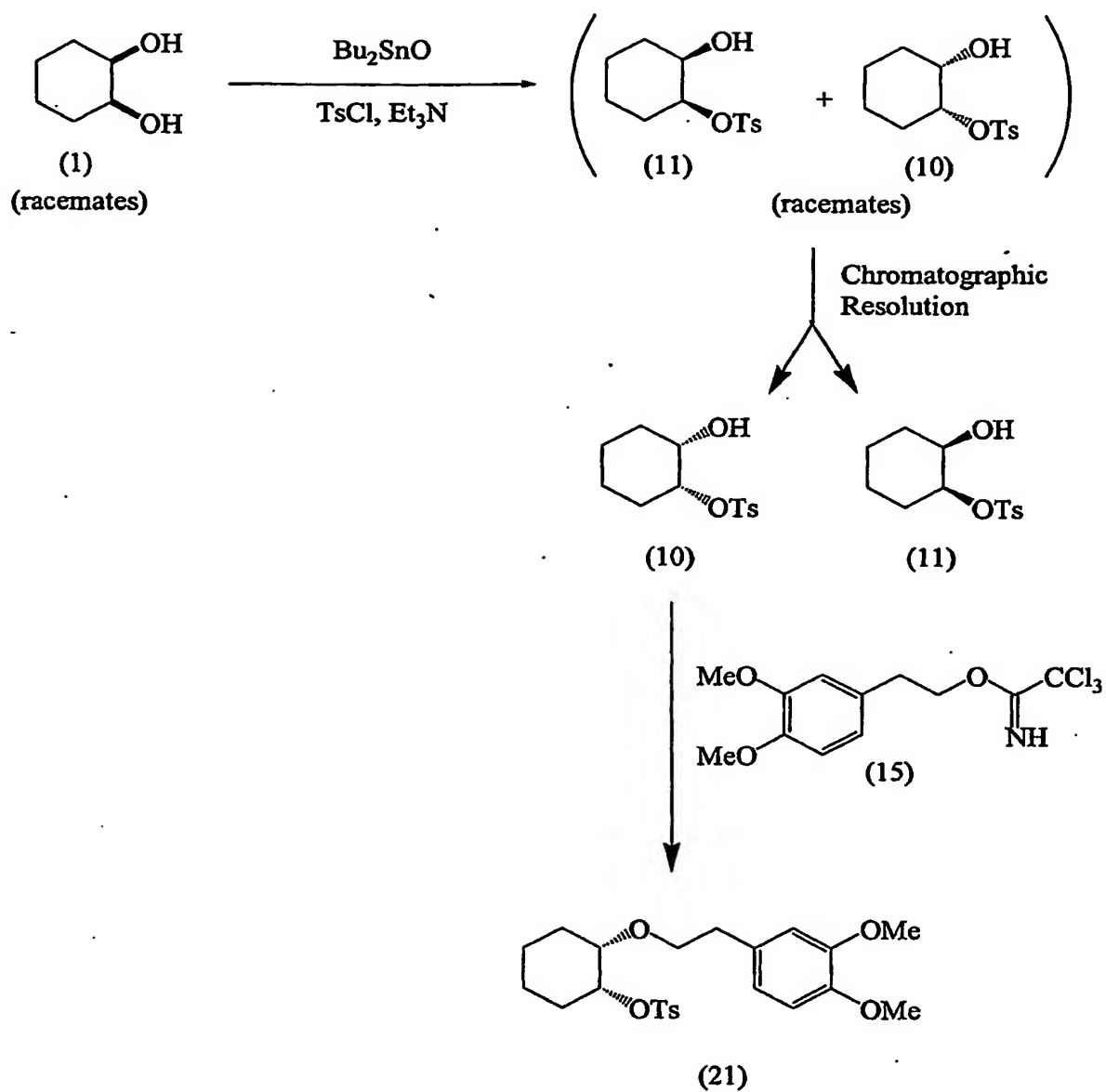
Scheme 38

Scheme 39

Scheme 40

Scheme 41



Scheme 42

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